SECOND SERIES VOL. 10, No. 5

BULLETIN

OF

THE NEW YORK ACADEMY OF MEDICINE

INCORPORATED 1851

MAY, 1934

PUBLISHED MONTHLY BY

THE NEW YORK ACADEMY OF MEDICINE

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New York, N. Y.

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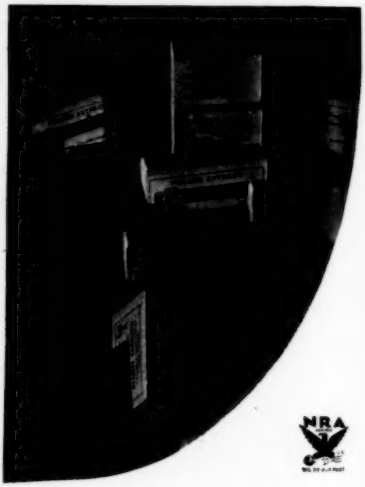

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VOL. 10 MAY, 1934 No. 5

ANNUAL GRADUATE FORTNIGHT
"DISORDERS OF METABOLISM"
October 23 to November 3, 1933

FLUID DISTRIBUTION AND EDEMA*

A. Ashley Weech

The student of equilibria in physiology will be impressed by a trend of thought in modern attempts to understand so-called "disturbances of balance". The human organism is coming to be regarded as a unit. It is recognized that in health the proper function of each part is dependent on normal function of a number of other parts, that a given symptom is rarely caused entirely by defect of a single organ, but results more commonly from numerous interrelated happenings in different regions of the body. Such a conception is essential for this evening's lecture "fluid distribution and edema". It will be necessary to examine data concerning a number of different factors or conditions which are involved in maintaining normal distribution or in promoting abnormal accumulation of fluid in the tissues. We must further attempt to discover in which manner the various factors are interrelated.

* Delivered October 26, 1933.

To facilitate orderly discussion I have tabulated the factors to be dealt with (Table 1). It may be assumed

TABLE 1.

THE REGULATION OF FLUID DISTRIBUTION IN THE BODY

A. FACTORS OPERATING AT THE WALL OF THE CAPILLARY.
   1. Colloid osmotic pressure of the plasma.
   2. Capillary blood pressure.
   3. Colloid osmotic pressure of tissue fluid.
   4. Mechanical pressure in the tissue spaces.
   5. Permeability of the capillary wall.

B. FACTORS WHICH MODIFY THE FORCES ON THE OUTSIDE OF THE WALL OF THE CAPILLARY.
   1. Lymph flow.
   2. Elasticity of the tissues.

C. FACTORS WHICH MODIFY THE FORCES ON THE INSIDE OF THE WALL OF THE CAPILLARY.
   1. Excessive proteinuria.
   2. Protein starvation.
   3. Venous obstruction and cardiac stasis.
   4. Variations in salt intake.
   5. The kidney.

to be axiomatic that fluid reaches the tissues by way of the blood stream, that is, by passing through the walls of the capillaries. For this reason the forces which govern the movement of fluid across the capillaries will be regarded as fundamental in controlling fluid distribution and I have grouped them together under "A". It is none the less true that the fundamental forces may be subject to modification from change in remote regions of the body and that the remote changes will often be the primary cause of disturbance. To consider all possible remote influences comprehensively would require far more time than is available and at the same time, because present knowledge is incomplete, be of dubious value. Those which I have listed under "B" and "C" have been selected because at the moment they seem to possess an importance deserving of emphasis. They include factors which modify the forces on the outside of the wall of the capillary and other factors which it is believed exert their effect on the forces within the capillary.

Our discussion may be opened suitably with two diagrams, introduced to make clear the action of osmotic forces in general. The test-tube-like structure in the first diagram (Fig. 1.) represents a membrane which may be com-

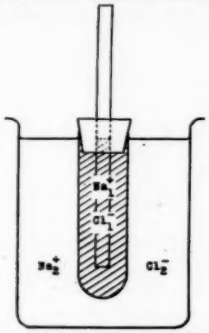

Fig. 1. Osmotic system in which only salts are present for which the membrane is permeable. No pressure is developed.

posed of collodion, parchment, or some similar substance. At the outset one concentration of sodium chloride is placed on the inside of the membrane and another concentration on the outside. The system is closed and connected to a manometer which can record any pressure within the membrane. The final state of affairs is depicted when the membrane permits the free passage of both sodium and chloride ions. By diffusion the concentrations of the two solutions are equalized and no osmotic pressure is developed. The final state is different (Fig. 2.) when within the membrane there is an additional large ion or molecule (R) which is unable to pass the membrane wall. Because the molecule cannot diffuse, ultimate equality of concentration on the two sides of the membrane is impossible and an osmotic pressure is developed, the magnitude of which is revealed by the height of the water column in the manometer. It is important to note that the osmotic pressure recorded by the system is independent of the concentrations of sodium and chloride and depends only on the concentration of R, that is, the molecule for which the membrane is impermeable.

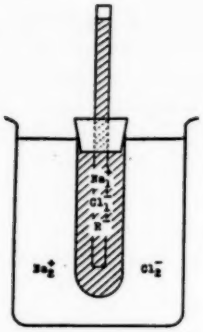

Fig. 2. Osmotic system in which there is present an additional molecule "R" for which the membrane is impermeable. Pressure is developed and measured by the height of the water column in the manometer.

A system similar to this one exists across the membrane wall of the capillaries which separate the blood plasma from interstitial fluid. The capillary is freely permeable to all of the substances dissolved in blood with the exception of protein which, therefore, exerts an osmotic pressure which endeavors to draw fluid from the tissue spaces into the blood stream. The total osmotic pressure of all the plasma crystalloids (sodium, potassium, bicarbonate, chloride, urea, etc.) lies between 5000-6000 mm. of mercury, that of the plasma colloid (protein) is normally from 20-30 mm. of mercury. Nevertheless, the property of free diffusion prevents the development of pressure due to crystalloids and only the colloid osmotic pressure is concerned in water distribution. Colloid osmotic pressure may be measured directly on samples of plasma outside the body by the use of a system containing a semipermeable membrane. It can also be calculated from the protein concentration of the plasma. For this purpose a knowledge of the total protein content is of little value. In chemical constitution the albumin molecule is much smaller than that of globulin, and, therefore, gram for gram, albumin gives more osmotically active particles than globulin.

Govaerts has estimated that 1.0 gram of albumin per 100 c.c. will produce an osmotic pressure of 5.5 mm. of mercury, whereas a similar concentration of globulin produces a pressure of only 1.4 mm. of mercury. With a knowledge of the albumin and globulin fractions it is possible to make an approximate calculation of the colloid osmotic pressure. In practice, because the pressure of globulin is small, osmotic pressure will be found roughly to parallel albumin concentration and the latter figure, obtained by direct analysis, is sometimes used as a measure of this force. Nevertheless, it is well to remember that rare cases are occasionally encountered in which a very high figure for plasma globulin renders the pressure from this fraction more important than that of albumin.

Colloid osmotic pressure, then, due chiefly to plasma albumin, tends to draw fluids into the circulation. In the normal individual this force is counterbalanced by a factor which appeared second on our list, namely, blood pressure within the capillaries. This blood pressure depends upon the force of the heart beat, vessel elasticity and hydrostatic effects. I have reproduced here (Fig. 3.) a diagram

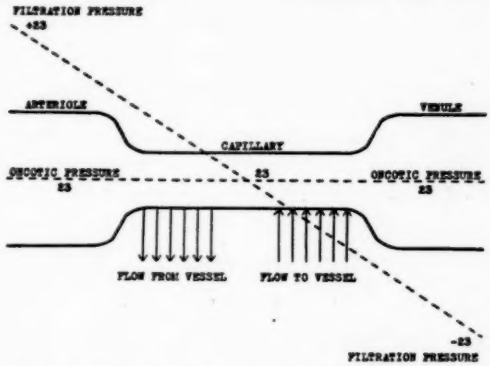

Fig. 3. The effect of mechanical pressure and colloid osmotic pressure on the flow of fluid through the wall of the capillary. After Christian (*J. A. M. A.*, 1931, *97*: 296).

taken from an article by Christian which may serve to illustrate the nicety with which the balance is maintained in health as well as the disturbances which lead to edema formation. The diagram portrays the course of events as blood flows from an arteriole, through a capillary, and into a venule. The dotted line running through the middle of the vessel indicates constancy of protein in the blood and, therefore, constancy of the colloid osmotic pressure, which in this instance is represented as having a normal value of 23 mm. of mercury. The diagonal dotted line indicates that mechanical blood pressure is falling as the blood continues its course through the capillary. On the arterial side of the capillary the pressure is seen to be greater than 23 mm. of mercury and on the venous side it is something less than 23 mm. A fall in pressure through this range is not an imaginary happening. Direct measurements by E. M. Landis of the pressure in single capillaries at the base of the human finger nail have shown that on the average the pressure falls from 32 mm. of mercury at the arterial end of the capillary to 12 mm. at the venous end. When we consider, then, the combined effect of the two opposing forces, it is seen that mechanical pressure is greater at the arterial side of the capillary and that osmotic pressure is greater at the venous side. The result will be, as is shown by the arrows, that fluid will first be expressed mechanically from the vessel and later returned by osmotic attraction. Such a to-and-fro flow of fluid has actually been demonstrated by Schade and Claussen on model capillaries constructed of collodion and perfused with normal serum. In health the balance between filtration and reabsorption is so nicely adjusted that no excess of free fluid can accumulate in the interstitial spaces. Such accumulation may, however, occur when the balance is disturbed. We shall see how this can be.

When a vein is obstructed mechanically or when generalized venous congestion has resulted from heart disease, a rise in pressure in the veins takes place which is reflected back into the capillaries. The rise in capillary blood pressure increases the filtering area of capillary wall

and decreases the resorptive area in such a way that more fluid leaves and less fluid returns to the vessel than under normal conditions. The disturbance brings about an increased accumulation of tissue fluid which, if great enough, will become manifest as palpable edema. A derangement of this sort is certainly one of the major factors in the production of cardiac edema.

On the other hand we are acquainted with several clinical diseases in which depletion of the blood protein and, therefore, of the plasma colloid osmotic pressure, is a conspicuous feature. The effect of the depletion is the same as an increase in mechanical pressure in bringing about a preponderance of filtration over reabsorption. If sufficient in degree it may also be the cause of edema. It can no longer be doubted that a major factor in the production of the edema of chronic Bright's disease is to be found in the plasma protein deficit which results from continued excessive proteinuria. There is also abundant evidence to show that prolonged protein starvation will lead to a similar depletion of the plasma protein and subsequently to edema. The relation between depleted plasma proteins and edema has been demonstrated by a number of investigators, chiefly by Dr. Peters and his colleagues in New Haven and by Drs. Moore and Van Slyke here in New York. It is shown clearly in Figure 4 in which have been charted some of our data concerning the relationship between plasma proteins and experimental edema in dogs. The black dots represent analyses of plasma made when edema was present and the open circles refer to estimations made before edema had developed or after it had disappeared. It is seen that edema rarely appeared before the albumin was depleted below 2 grams per 100 c.c., that it was more often present than absent when the albumin was between 1 and 2 grams per 100 c.c., and that below 1 gram edema was always present. The relative importance of albumin in controlling osmotic pressure is shown by the absence of any correlation between globulin and edema and by the relatively slight correlation between total protein and edema. Charts

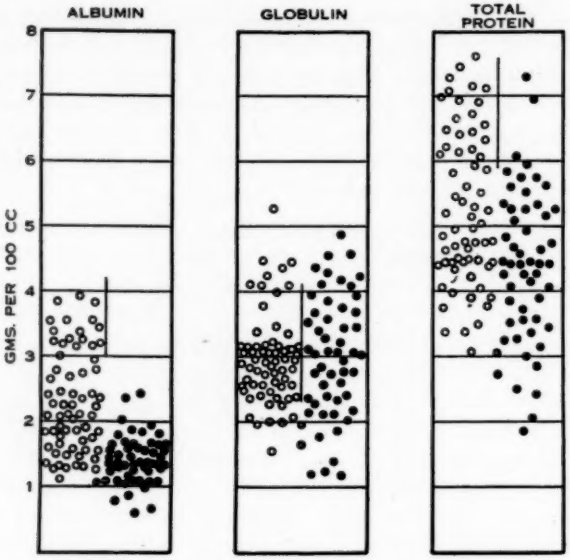

Fig. 4. The relation between plasma protein concentration and edema in dogs. Open circles indicate estimations made when no edema was present; black circles indicate estimations made when edema was present; vertical lines in the middle of each column indicate the range of normal variation. After Weech, A. A., Snelling, C. E., and Goettsch, E. (*J. Clin. Invest.*, 1933, *12:* 193).

similar to this may easily be prepared from data obtained on humans although with humans the level of albumin associated with the appearance of edema is somewhat higher than with dogs. According to Moore and Van Slyke it lies between 2.3 and 2.7 grams per 100 c.c.

It is seen, then, that disturbance of a balance between two opposing forces on the inside of the capillary may take place so as to favor edema formation. The credit for recognizing first the importance of this balance belongs to Starling in 1896. The theory of Starling is concerned chiefly with forces arising within the capillary. It is now necessary to inquire whether extramural forces need not

also be considered in evaluating the movement and distribution of fluid. For it is possible to conceive of mechanical and osmotic forces within the tissue spaces as well as within the capillaries. Unfortunately exact knowledge of these forces is still fragmentary. It is pertinent, however, to observe that, when the balance between intracapillary forces is disturbed in such a way that filtration occurs in excess of resorption, fluid does not continue to enter the tissue spaces in unlimited quantities. It is apparent that distending the tissues with fluid creates a certain amount of back-pressure and that this in time compensates for the disturbed balance and leads to the establishment of a new equilibrium. The exact magnitudes of tissue pressure are yet unknown. It is certain that it cannot rise higher than capillary blood pressure for such an increase would lead to collapse of the vessels. Moreover, we shall see in a moment, that tissue pressure probably varies continuously during physical activity and approaches constancy only during complete rest. It may be stated, however, that the effective mechanical force operating across the wall of the capillary is not represented by capillary blood pressure alone but rather by the difference between this pressure and mechanical tension in the tissues. In an analogous manner we must suppose the effective osmotic pressure to be the difference between osmotic pressure on the inside and on the outside of the wall of the capillary. Again, however, we are faced by a paucity of information concerning the concentration of protein in tissue fluid for during health this fluid exists in such small amounts that it cannot be obtained for analysis and its composition is really unknown. Although it is true that so-called filtration edemas, such as occur in chronic nephritis and malnutrition, are characterized by an edema fluid of extremely low protein content, it is dangerous to infer from this finding that normal tissue fluid is to a like extent protein-free. Within the last few years Drinker and Field of Harvard have given reasons for their belief that lymph and tissue fluid possess "an approximate degree of identity" and have shown that lymph contains more protein than has

usually been supposed to exist in tissue fluid. Although there is not time in this place to enter upon a discussion of the relationship between these two fluids, it is likely that the protein content of normal tissue fluid is not negligible.

As an aid to visualization of the interplay between forces on both sides of the capillary wall, it is possible to express the relationship during periods of equilibrium, that is, at times when edema is neither advancing nor receding, in equation form:

$$S - I = C - T$$

During these periods the total forces on the inside of the capillary must equal those on the outside, a relationship which the equation expresses by representing the difference between the colloid osmotic pressure of serum (S) and the colloid osmotic pressure of tissue fluid (I) as equal to the difference between capillary blood pressure (C) and mechanical pressure within the tissues (T). We have already seen that a reduced osmotic pressure of serum or an increased blood pressure in the capillaries favors the filtration of more fluid toward the tissues. The equation indicates that a similar effect might result from an increase in the osmotic pressure of tissue fluid or from a decrease in tension within the tissues.

The protein content and, therefore, the colloid osmotic pressure, of tissue fluid are determined principally by the degree to which the capillaries are permeable to protein. In certain morbid processes the permeability may be greatly increased and an edema result in which the protein content of the edema fluid approaches that of the plasma. Allergic edema and the edema of inflammation belong in this group. The process is essentially a simple one in which blood plasma, as such, infiltrates the tissues. It is fundamentally different from that which gives rise to nephrotic edema, nutritional edema, or cardiac edema. Indeed, recently collected data suggest that those forms of edema which are characterized by edema fluids of low protein content may be associated with capillaries whose normal permeability to protein has been appreciably de-

creased rather than increased. If this is true, the edema has occurred in spite of changes in the capillary wall which might be looked on as an attempt at compensation. The evidence which has led us to this inference of decreased permeability of the capillaries in filtration edema may be presented briefly. Table 2 presents the protein concentra-

TABLE 2.

PROTEINS IN LYMPH AND SERUM OF NORMAL AND EDEMATOUS DOGS

NORMAL ANIMALS				EDEMATOUS ANIMALS			
Dog	Lymph Protein per cent	Serum Protein per cent	Serum Prot. / Lymph. Prot.	Dog	Lymph Protein per cent	Serum Protein per cent	Serum Prot. / Lymph. Prot.
841	1.92	6.83	3.6	992	0.07	2.10	30.0
842	2.93	7.40	2.5	6	0.39	2.60	6.7
895	0.74	5.60	7.6	58	0.11	2.49	22.6
949	1.25	6.04	4.8	840	0.13	2.88	22.2
950	3.45	7.89	2.3	91	0.46	3.32	7.2
100	0.66	5.70	8.6	23	0.17	3.38	19.9
58	0.90	5.70	6.3	5	0.22	3.24	14.7
69	1.26	5.77	4.6	131	0.04	3.20	80.0
91	1.89	6.38	3.4	838	0.37	3.00	8.1
92	1.40	5.73	4.1	806	0.36	3.00	8.3
131	1.17	5.99	5.1				
840	1.46	5.07	3.5				
Mean (Geometric)	1.41	6.13	4.4	Mean (Geometric)	0.18	2.89	16.1

tions of subcutaneous lymph and blood serum in a series of normal dogs which are to be compared with similar analyses in a group of edematous dogs. I may mention that the protein of lymph is derived from the blood and represents material which has filtered through capillaries. When the protein of serum decreases, other things being equal, we should expect a proportionate decrease in the protein of lymph. With the animals from which the figures in the table were derived the experimental procedure responsible for edema reduced the serum protein to about half its original value. The reduction in lymph protein, however, occurred at a much more rapid rate,

the mean value in the edematous animals being one-eighth that in the normal animals. The disproportionate reduction is likewise reflected in a striking rise in the ratio of serum protein to lymph protein. This change cannot be explained simply on the basis of an increase in filtration pressure but can be accounted for by supposing that a decline in the protein of serum is associated with a diminished permeability of the capillaries.

An analogous conclusion is suggested by the data presented in Table 3. When a cannula is introduced into one

TABLE 3.

FLOW OF LYMPH FROM THE EXTREMITIES OF DOGS AFTER ESTABLISHMENT OF CONSTANT RATE

NORMAL ANIMALS			EDEMATOUS ANIMALS		
Dog	Serum Osmotic Pressure mm. of Hg	Rate of Flow c.c. per 10 min.	Dog	Serum Osmotic Pressure mm. of Hg	Rate of Flow c.c. per 10 min.
91	24.3	0.6	58	8.9	0.4
100	17.6	0.7	992	6.7	0.6
92	18.5	1.1	6	9.6	1.1
840	19.8	1.5	6	9.6	1.3
131	21.6	1.6	992	6.7	1.4
58	22.1	4.8	840	7.6	1.7
			91	11.8	1.7
			131	10.4	2.4
			23	9.9	2.6
			58	8.1	3.0
			23	9.9	3.6
			5	10.1	5.3
Average	20.7 ± 0.6*	1.71 ± 0.39*	Average	9.1 ± 0.3*	2.09 ± 0.26*

*Probable error of mean.

of the peripheral lymphatics and the flow of lymph stimulated by keeping the extremity in motion, the rate of flow is at first variable but after a time becomes constant and

may remain so for several hours. During the period of constant flow the observed rate must correspond to the production of fresh lymph, that is, to the rate of capillary filtration in the extremity. In the table there have been recorded a number of examples of the rate of lymph flow when constancy was reached in both normal and edematous animals. The range of variation is seen to be approximately the same in the two groups, that is, between 0.6 and 4.8 c.c. per 10 minutes in the normal animals and between 0.4 and 5.3 c.c. per 10 minutes in the edematous animals. The average rate of flow for the edematous dogs is very slightly greater than for the normal dogs. The data for serum osmotic pressure show a reduction from 20.7 to 9.1 mm. of mercury; the reduction must have caused a considerable rise in filtration pressure, and we are forced to explain the failure to observe a significant increase in the rate of filtration from the capillary. The failure can be accounted for by assuming again that the reduction in serum proteins in the edematous animals has been accompanied by diminished capillary permeability and, therefore, by a restricted rate of capillary filtration.

Until now our discussion has dealt almost exclusively with forces and conditions controlling the filtration of fluid across the capillaries. We have noted in passing that remote influences such as protein starvation, excessive proteinuria, or cardiac stasis may disturb the balance of forces at the wall of the capillary and lead to edema. The manner of action of these influences is direct and relatively easily understood. We must now consider briefly several less apparent factors which may likewise modify conditions around the capillary.

Chief among the factors which control conditions on the outside of the capillary are the minute radicles of the lymphatic system. To understand their action it is necessary to bear in mind (1) that the radicles are as numerous and as diffusely distributed as the blood capillaries, (2) that their connection with the intercellular and intercapillary tissue spaces is most intimate, and (3) that they

possess no intrinsic mechanism for maintaining a continuous flow of fluid through their lumens. The lymphatics are abundantly supplied with valves which when massaged from the outside act as so many small pumps and establish an intermittent type of circulation which is active when the animal is moving and which ceases entirely during complete rest. At times of complete inactivity, therefore, fluid accumulates in the tissue spaces with a rise in tissue pressure until capillary filtration and reabsorption are equal and further accumulation is stopped. It is to this equilibrium of physical inactivity only that the equation expressing the balance between forces about the wall of the capillary applies. When the muscles are moved the lymphatics are activated at once, fluid is withdrawn from the tissue spaces with a corresponding fall in tissue pressure, and the balance around the capillary is disturbed so as to increase capillary filtration. A continuous circulation of fluid is thereby created from the capillary, through the tissue spaces, and into the lymphatics. From one point of view, then, the lymphatics can be looked upon as a major factor in controlling pressure within the tissue spaces and thereby indirectly influencing the volume of capillary filtrate. It is clear that tissue pressure cannot rise to a higher value than that necessary to render capillary reabsorption equal to filtration. It is likely, however, that more or less intermittent activity of the lymphatics serves constantly to maintain tissue pressure at values somewhat lower than the maximum.

Another important function is served by the lymphatics. We have seen that the capillaries are not completely impermeable to protein and it is evident that in the absence of some regulatory mechanism any degree of permeability, however slight, would in time lead to equilibrium of protein concentrations on the two sides of the membrane. For, in this case the constant diffusion of protein irrespective of the movement of fluid is concerned. The regulatory mechanism is supplied by the lymphatics which by removing fluid mechanically from the tissue spaces prevent the lapse of time necessary for equality of protein concen-

tration with the blood. The edema which results from lymphatic obstruction in all probability is not caused by the damming back of fluid in the tissues but rather results from the fact that the mechanism for maintaining a tissue fluid of relatively low protein content has been destroyed. The end result, an edema fluid of high protein content, is similar to that which develops when the permeability of the capillaries has been greatly increased by inflammatory disease. I may mention that the edema of tropical elephantiasis is supposed to result from blockage of the lymphatics with filariae and that Drinker and Field have succeeded in producing a chronic localized edema in dogs by utilizing an injection mixture containing quinine and powdered silica to obstruct the draining lymphatic trunks.

One other factor capable of modifying conditions on the outside of the capillary wall remains to be mentioned. I refer to the elasticity of the tissues themselves. We have seen that a change in the forces about the capillary in the direction which favors a preponderance of filtration over reabsorption is ultimately compensated by a rise in pressure in the tissue spaces. It is clear that the rise in pressure will create a stress which must be borne by the interstitial tissues and that no phenomenon of edema could exist if the tissues were incapable of yielding to increasing stress. Unfortunately little information exists concerning the manner whereby they do yield. It is certain that they are not perfectly elastic, that is, that equal increments of stress do not produce equal increments of stretching. The most recent work of Holland and Meyer would suggest that they are plastic in nature, exhibiting very slight elasticity under moderate stress, yielding suddenly to greater stress, and being unable to return immediately to the original state on withdrawal of the stress. The nature of this "tissue elasticity" is too obscure to warrant more lengthy discussion. It is mentioned because a change in its character would be expected to alter the distribution of fluid.

Two phenomena of great importance remain for discussion. Both are familiar to every clinician, both have contributed to our therapeutic armamentarium, both have been studied extensively on the ward and in the laboratory, and yet both are still shrouded in mystery for him who wishes to know "the how and the why". I refer to the hydropigenous action of salt on the edematous state and to the sudden occurrence of diuresis with loss of edema in nephrotic patients when analyses fail to indicate any significant increase in the proteins of the serum. Because our discussion must be brief I shall introduce the phenomena by presenting the results of one of our experiments with dogs.

Figure 5 presents the record of an animal which was

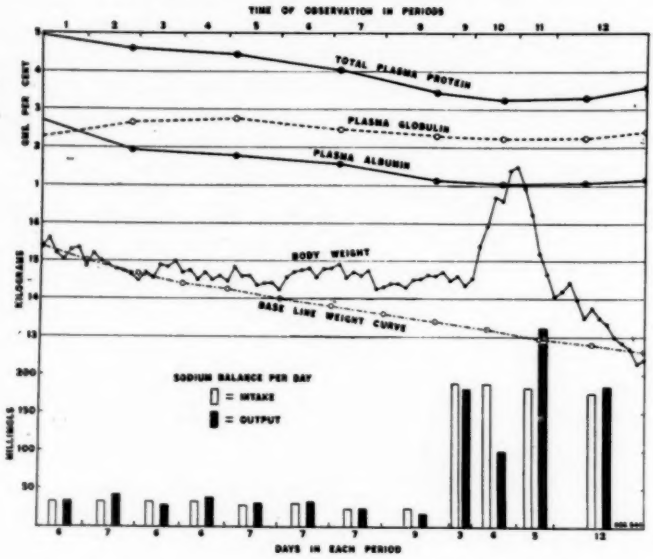

Fig. 5. Development of nutritional edema in a dog. The experiment reproduces two phenomena which are often observed in human patients—(1) marked retention of fluid following the ingestion of salt, and (2) spontaneous diuresis.

maintained 81 days on a diet deficient in protein. During the first 8 metabolism periods (55 days) the diet contained about 30 millimols of sodium chloride daily; for the remainder of the experiment the salt intake was increased to about 200 millimols daily. The diet is seen to have led to gradual lowering of the plasma albumin concentration. The broken line which is marked "Base Line Weight Curve" was drawn by subtracting from the animal's initial weight successive decrements calculated from the known loss of nitrogen. Deviations above this line of the curve of true body weight may be regarded as evidence of water retention. It is seen that some retention occurred early in the experiment even when the diet contained very little salt. Examination of the dog during this stage showed that the tissues of the groin and abdominal wall had become full although there was no palpable edema. The institution of high salt feeding was followed by a series of changing responses which are shown both by the weight curve and by the columns indicating the sodium balance—first a 3-day period of approximate salt equilibrium associated with a flat weight curve, second a 6-day period during which much salt was retained and the body weight increased 3 kilograms and massive edema appeared, and finally a 5-day period and a 12-day period during which the balance was negative and rapid loss of weight with subsidence of edema occurred. The experiment was terminated at this time because the animal's condition seemed critical. After a short period on a good ration she made an excellent recovery.

In this experiment, then, there have been reproduced both of the phenomena in which we are interested, namely, marked fluid retention resulting from the ingestion of salt, and spontaneous diuresis with loss of edema at a time when it might seem that the stage was set for further retention. By way of explanation it is suggested that a sudden increase in the quantity of ingested salt leads to an at least temporary increase in the volume of the blood. Such an increase implies some dilution of the plasma proteins and is possibly attended by a slight rise in capillary

blood pressure. Either of these changes would disturb the balance of forces so as to increase filtration from the capillaries and provide an increment in the mechanical stress to be borne by the tissues. There can be no doubt that the tissues of the healthy animal are able to withstand a stress of this magnitude. They may yield slightly and so permit a small increase in the total volume of interstitial fluid but edema does not result. In the animal with depleted plasma proteins, however, the increment of stress may be delivered at a time when the elastic strength of the tissues is near the yielding point. Even a small increment at this time could pass the limit of elastic strength, at which point the rapid accumulation of edema fluid would begin and go on until a stage was reached when the tissues were not able to hold more fluid. At this stage, or possibly even before, the renal mechanism responsible for diuresis may be called into action. In the experiment before us the curves for the plasma proteins suggest that diuresis caused a reduction in blood volume for we find that both albumin and globulin rose without change in their ratio. It is not possible to think of this rise as having resulted from actual protein regeneration. Now, the removal of fluid from the blood stream as well as from the tissues incriminates the kidney as being primarily responsible for the diuresis. For, if the motivating factor had been one which caused overloaded tissues to discharge their fluid we should not have expected the circulating blood to give up more than the extra amount of fluid received. In this case, then, the establishment of renal diuresis was sufficient to annul completely the tendency to fluid retention caused by the low serum proteins. The sequence of events involved may possibly have been as follows: (1) renal changes initiating diuresis, (2) decrease in the volume of the blood, (3) increase in the concentration of protein in the plasma, (4) a possible lowering of capillary blood pressure, and (5) discharge of fluid from the tissues into the blood stream.

The nature of the change in the kidney responsible for diuresis cannot concern us here. Indeed, it is far from established that renal change is either always or even most

often the cause of diuresis. On the contrary evidence exists which suggests that the process may sometimes be initiated by changes of an unknown nature in the tissues. And similarly it is possible that the steps involved in the retention of fluid which follows the administration of salt are not so simple as those which have been pictured. It is necessary, then, to confess much ignorance and having so confessed I trust you will not judge me harshly for having attempted to provide that which claims to be no more than an *understandable* basis for the phenomena.

To conclude and summarize: I have set before you this evening a list of factors which are concerned in fixing the distribution of fluid between the plasma and the interstitial spaces. Primary consideration has been given to those forces which control directly the movement of fluid across the capillary. The forces include the colloid osmotic pressure of the serum, the intracapillary blood pressure, the colloid osmotic pressure of tissue fluid, and mechanical pressure in the tissue spaces. During health the balance between the opposing forces is so beautifully adjusted that appreciable quantities of free fluid do not collect in the intercellular spaces. A change, however, in the direction which favors the filtration of fluid from the capillaries means an increment in the mechanical stress which the interstitial spaces must withstand and may lead to the development of edema. The existence of an effective osmotic force across the capillary is immediately dependent upon relative impermeability of its wall for protein. We have seen that edema may result from loss of this impermeability and that the loss may be due to allergic disease or to inflammation. Conversely, the degree of impermeability may be increased, and so provide a partial compensatory mechanism, in conditions in which the colloid osmotic pressure of plasma is abnormally low. We have further seen that the osmotic pressure of tissue fluid depends in large part upon the constancy with which protein is removed from the tissues via the lymphatics and that mechanical pressure in the intercellular spaces varies both with the activity of the lymphatics and with the elasticity of sur-

rounding tissue. I have pointed out that remote influences such as an excessive loss of protein in the urine or prolonged maintenance on a diet deficient in protein may lead to depletion of the serum proteins and therefore to a decrease in the effective osmotic pressure of plasma, that venous obstruction or venous stasis from myocardial failure may raise blood pressure within the capillaries, and finally have suggested that both forces on the inside of the wall of the capillary may be altered by changes within the kidney or by variations in the quantity of sodium chloride ingested.

CONGENITAL ANOMALIES OF METABOLISM WITH SPECIAL REFERENCE TO CYSTINURIA AND MYOPATHIES*

ERWIN BRAND

"Inborn errors of metabolism", has become a familiar term in medicine, since Garrod[1] first used it in his Croonian Lectures to designate a group of rare metabolic diseases, which he characterizes as follows: "Some of them are certainly, and all of them are probably, present from birth. The chemical error pursues an even course and shows no tendency to become aggravated as time goes on, and they are little likely to be influenced by any therapeutic measures at our disposal. Yet they are characterized by wide departures from the normal of the species far more conspicuous than any ordinary individual variations, and one is tempted to regard them as metabolic sports, the chemical analogues of structural malformations." Among these conditions, Garrod includes the following:

Albinism	Cystinuria
Pentosuria	Congenital Porphyrinuria and
Alkaptonuria	Congenital Steatorrhoea.

Because of the familial character of muscular dystrophy and the striking disturbance in creatine and creatinine metabolism observed in these patients, and because of the possibility that it may be metabolic in nature, we will consider this disease in the group of inborn errors of metabolism.

The limited time at one's disposal renders it unfeasible to discuss in any detail the various metabolic conditions which have been enumerated. It was thought, therefore, that it would be preferable to consider only a few of these diseases and I will restrict myself accordingly to cystinuria and myopathies.

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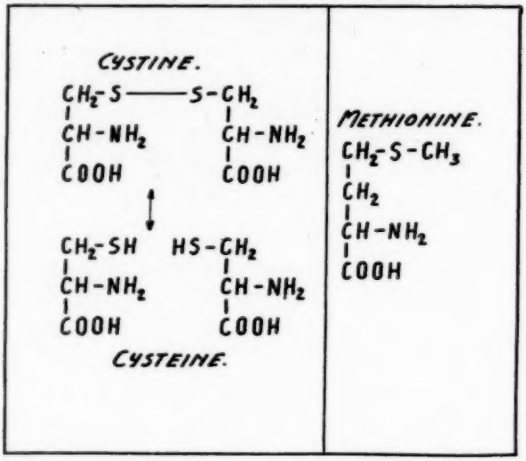
* Delivered October 27, 1933.

I. Cystinuria

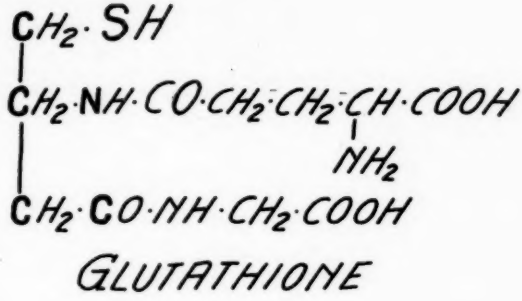
Cystine was discovered in 1810 by Wollaston, who isolated it from a urinary calculus. Almost 90 years elapsed before it was found that many proteins yielded this amino acid upon acid hydrolysis. Cystine contains sulfur in its molecule in the form of an SS or a disulfide linkage. Cystine can be reduced by various agents to two molecules of cysteine, which now contains an SH group. Cysteine on the other hand may be oxidized to cystine. Cystine remained for many years the only sulfur containing constituent of proteins. Only recently, another sulfur containing amino acid, methionine, was discovered.



Cystine is one of the amino acids essential in nutrition, *i.e.*, it has to be supplied with the food because the animal body is not able to synthesize it. Cystine or cystine derivatives occur in all tissues. Particularly large amounts are present in the keratinous tissues such as horn, nails, hair and epidermis.

Of great importance is the recent discovery of Sir Frederick Gowland Hopkins, that cysteine exists in all cells in the form of a tripeptide, glutathione. Three amino

acids, cysteine, glycine and glumatic acid, combine to form the glutathione molecule. Glutathione plays an important role in the oxidation and reduction mechanisms of most cells.



GLUTATHIONE

A brief analysis of our knowledge concerning normal sulfur metabolism seems advisable before entering into a discussion of its disturbance in cystinuria. A small portion of the sulfur is present in saliva and in gastric juice as thiocyanate and in the bile as taurine. Some sulfur occurs in the tissues, especially in liver and blood, as glutathione. Most of the sulfur, however, is found as a constituent of the proteins of food and tissues.

Only small amounts of sulfur are excreted in the alimentary canal and almost all of the sulfur of food and tissues is oxidized to sulfuric acid and excreted in the urine as inorganic sulfate. Part of these sulfates appears in the urine combined with certain aromatic or other constituents in the form of ethereal sulfates. The sum of the inorganic and ethereal sulfates is designated as total sulfates and makes up about 90 to 95 per cent of the total sulfur excreted in the urine. The rest consists of sulfur compounds like thiosulfate, thiocyanate and other organic sulfur compounds which are, as yet, not very well known. This fraction of the urinary sulfur is called neutral or organic sulfur and constitutes usually only about 5 per cent of the total urinary S.

PARTITION of URINARY SULFUR.
(AVERAGE NORMAL DIET.)

	TOTAL SULFATE %	NEUTRAL SULFUR %
NORMAL	95	5
CYSTINURIC (TYPICAL CASE)	55	45

In cystinuria, we have an excretion of cystine in the urine which excretion may amount to from ½ - 2 gms. daily. Cystine, being an organic sulfur compound, is determined as part of the neutral sulfur fraction of the urine. In a case of cystinuria we will, therefore, note a decided increase in the neutral sulfur fraction of the urine, which increase however is at the expense of the sulfate excretion, which is decreased. Thus the sulfates may amount to only 55 per cent instead of 90 per cent of the total sulfur, while the neutral sulfur may be as high as 40 per cent or 50 per cent. The decrease of sulfate excretion is entirely at the expense of the inorganic sulfates, the excretion of ethereal sulfates remains normal.

Cystinurics always excrete inorganic sulfates and only part of the total sulfur of the catabolized proteins is excreted as cystine. The error in metabolism, in Garrod's words, is never complete. A possible explanation for this "incompleteness" of the metabolic error may be found in some of our recent experiments which will be discussed shortly.

The study of cystinuria has been facilitated in recent years by the development of reliable qualitative and quan-

titative methods for the determination of cystine in the urine. Among the latter the Folin test in its various modifications and the highly specific Sullivan reaction are worthy of mention.

Regarding the incidence of cystinuria it is interesting to note that up to 1916 we find only 107 cases of cystine calculi reported in the period of more than a century after Wollaston's original observation. Since then the number of cases of cystinuria reported has been large and H. B. Lewis[2] found at least 20 definite cases in an examination of about 11,000 urines of healthy young men and women.

The cystinuric loses appreciable amounts of cystine daily in the urine, apparently however without any ill effect. The only complication as far as one knows is the formation of cystine stones in the urinary tract, cystine being a very insoluble amino acid, its solubility in water being only 1 part in 10,000.

The cystine stones tend to form in the kidney pelvis, from which they may pass through the ureter into the bladder. The percentage of cases with stone formation is not as high as one would expect and some authors claim that only 3 per cent of cystinurics form stones. Cystine stones weighing as much as 50 gms. have been found, and they have been reported in children even as young as two years of age. It is not unusual that a kidney is completely blocked and destroyed by cystine stones.

In order to prevent or minimize stone formation in cystinuria a low protein diet and alkali administration have been frequently advocated. In this connection an observation by Dr. G. F. Cahill of the Squier Urological Clinic of the Presbyterian Hospital on a patient suffering from cystinuria with stone formation may be of interest. The right kidney of this patient was removed because it was completely destroyed by stones; X-ray examination showed no stones in the left kidney and ureter. The patient was then put on a low protein diet plus alkali. About three months following the removal of the right kidney a cystine

INCREASE of CYSTINE in CYSTINURIC URINE on STANDING.

URINE SPECIMEN	A			B		
AGE of SPECIMEN	3 hrs.	8 hrs.	24 hrs.	3 hrs.	8 hrs.	24 hrs.
CYSTINE — mgs.	101	123	157	213	278	338
CYSTINE — % of SULLIVAN NEUTRALS	43	53	67	59	76	92

stone was observed in the left ureter. Seventeen days later the stone had approximately doubled in size and had to be removed by surgical means. During this entire period the patient had been on a low protein diet plus alkali.

For a number of reasons, which time does not permit me to discuss, we believe that both a low protein diet and alkali administration are of questionable value in cystinuria. It is our opinion that cystinuric patients suffering from stone formation should receive in their diet a sufficient amount of protein to satisfy their demands for nitrogen and for the important essential amino acids including cystine. About 50-70 gms. of protein of good nutritional value should be given, depending on age and weight of the patient.

In regard to the form in which cystine may be excreted in cases of cystinuria it may be of interest to present an observation which was made a few years ago[3]. It was found with the aid of the Sullivan reaction, which is highly specific for cystine, that a fresh cystinuric urine yielded less cystine than the same urine after it had been standing for 24 hours.

This finding was interpreted as indicating that in cases of cystinuria there may be excreted not free cystine but a complex which decomposes in the urine with the liberation of free cystine. In regard to the nature of this compound

no information is available, but we are speculating now about the possibility that it may be a cysteine compound, containing perhaps an ether or thioxyester linkage.

On a standard diet cystinuric patients excrete daily fairly uniform amounts of cystine. An increase in the protein intake is followed by an increase in the cystine excretion and a decrease in the protein intake is followed by a decrease in the excretion of cystine. However, if free cystine is fed to a cystinuric, no additional cystine appears in the urine, and all of it is burned to sulfuric acid being excreted as such. It has been observed time and again that the cystinuric patient oxidizes free cystine to about the same extent as the normal person and excretes it as inorganic sulfate. Investigators have always been at a loss to explain how a cystinuric patient, on the one hand, can oxidize the free amino acid cystine when it is fed as such and on the other hand, cannot oxidize the same amino acid when it is given in combined form as protein.

Dr. Cahill, Dr. Harris and I had recently the opportunity to carry out a series of metabolic investigations on a cystinuric patient of the Squier Urological Clinic of the Presbyterian Hospital. The work was aided by grants from the Committee on Scientific Research of the American Medical Association[4].

In these experiments a cystinuric patient was kept for a period of approximately four months on a standard meat free diet and his urine analyzed daily for various nitrogenous and sulfur constituents. In addition the cystine sulfur was determined by both the Folin and the Sullivan methods.

During experimental periods of 3 days each the following compounds were fed in the quantities (equivalent amounts of sulfur) indicated: cystine (6.4 gms.), glutathione (16 gms.), cysteine HCl (8.8 gms., neutralized) and dl-methionine (8 gms.). The experiments were carried out in triplicate except the one with glutathione which was repeated only once.

The results may be summarized as follows:

Cystine experiments showed that 94 per cent of the extra sulfur was excreted as inorganic sulfate and that there was no rise in the excretion of cystine.

Glutathione experiments showed that 80 per cent of the extra sulfur was excreted as inorganic sulfate and that there was a slight rise in the excretion of cystine which amounted to 9 per cent of the extra sulfur.

Cysteine experiments showed that only 34 per cent of the extra sulfur was excreted as inorganic sulfate while there was a large increase in the excretion of cystine, continuing for several days after the feeding, which increase in cystine excretion accounted for 66 per cent of the extra sulfur. The analyses also indicated that additional cystine and not cysteine was being excreted.

dl-Methionine experiments showed that only 34 per cent of the extra sulfur was excreted as inorganic sulfate while there was a large increase in the excretion of cystine continuing for several days after the feeding, which increase in cystine excretion amounted to 47 per cent of the extra sulfur; there was also a definite increase in the excretion of undetermined (non-cystine) neutral sulfur which amounted to 19 per cent of the extra sulfur. The analyses again indicated that additional cystine and not cysteine was being excreted.

These experiments tend to show that the metabolism of cystine may be quite different from that of cysteine and that these two compounds are not as interchangeable in intermediary metabolism as has been assumed generally. They further show that the metabolic behavior of an amino acid may vary markedly depending upon whether it is catabolized as a free amino acid (cysteine) or in combined form as a peptide (glutathione). The experiments also indicate that methionine may be metabolized via cysteine. Experiments by Jackson and Block[5] and by White and Lewis[6] have recently established a close metabolic interrelationship between methionine and cystine.

The above mentioned authors are inclined to interpret their findings as indicating that methionine may spare cystine. Our experiments however establish the possibility that in intermediary metabolism methionine, under conditions, may be transformed directly or indirectly into cystine via cysteine.

The finding that cystine is excreted following the administration of cysteine indicates the possible role of the kidney in the oxidation reduction mechanism of the SS-SH system.

It appears that the cystine which the cystinuric excretes in the urine may be derived, in part or in whole, from that portion of the protein sulfur which is present in the protein molecule in the form of methionine. Further experiments will be necessary to determine to what an extent cystinuria is primarily a disturbance in methionine metabolism.

The possibility of a disturbance in glutathione synthesis in cystinuria should be considered. This view would be in keeping with the aspects of intermediary protein metabolism indicated in a previous publication[7].

II. Myopathies

Although general attention has been directed to the myopathies since Aran's communication published in 1850 and much has been written regarding them, our insight into the pathogenesis of this group of diseases has remained rather superficial and controversial. The concept of the myopathies is as yet not firmly established and the characteristics of the various groups are not clearly delineated, nor their dividing lines sharply drawn.

In an editorial discussion[8] on the muscular dystrophies in the Lancet in 1925, it was pointed out that one is not likely to reach any rational conception of treatment of the myopathies from clinical studies alone, and that chemical investigation in these conditions is an uncultivated field which will repay any labor that is spent on it.

It was shown by Folin[9] in 1905 and a little later by Klercker[10] that the normal adult excretes from day to day uniform amounts of creatinine in the urine but no creatine or only very small amounts, especially in the case of the female. It was also shown that these findings are not readily altered in the normal person by the level of the protein in the diet. It has been claimed that the amount of creatinine excreted bears some relation to muscular mass but not to the tone or activity of the muscles. The significance of this relationship is as yet not entirely clear. Although some believe that creatinine is related to the amount of creatine or creatine phosphoric acid stored in the muscles, the origin of creatinine from this source is by no means established, nor is the mechanism of its formation known[11]. There appears to be, however, an intimate relation to carbohydrate metabolism.

The relative amount of creatine in the urine is materially increased during childhood up to between 10 and 15 years of age and also in the adult during certain physiologic processes such as lactation or in a variety of pathologic processes such as fever, starvation, severe diabetes or other conditions associated with deprivation of carbohydrates, severe exophthalmic goiter and certain myopathies.

Rosenthal[12] knew as early as 1870 that certain myopathies were associated with a disturbance in creatinine excretion as indicated by a diminished daily output. This observation was confirmed by various investigators and particularly by Spriggs[13] using the improved Folin method for creatinine determination.

P. A. Levene and Kristeller[14], in 1909, working in Montefiore Hospital, carried out quantitative studies on the urine of patients with various muscular disturbances and found that in cases of progressive muscular dystrophy there was not only a low creatinine but also a high creatine output. They further observed that increased amounts of protein in the diet increased the amount of creatine excreted by such patients. And unlike normal adults, these persons also eliminated a large percentage of small

amounts of creatine administered orally. (Such diminished tolerance to creatine is present in other types of creatinuria, and when present may be influenced by the level of the protein intake.)

Gibson and Martin[15] (1922) tried to determine what constituent of the protein molecule produced the rise in creatine excretion in muscular dystrophy but without any success.

Early in 1928 Dr. M. Sandberg and I in the laboratory division of Montefiore Hospital under Dr. David Marine started to cooperate with Dr. M. M. Harris of the Medical Service of Dr. B. S. Oppenheimer on an extensive metabolic investigation on the creatine and creatinine metabolism of patients with muscular dystrophy. The work was continued later by Dr. Harris and myself at the New York State Psychiatric Institute and Hospital.

The patients were kept under standardized conditions over a prolonged period of time and their urine analyzed daily for creatine, creatinine and other constituents. The effect of oral administration of various substances which were superimposed on the diet was studied.

It was found[16] on repeated experiments that glycine produced an appreciable increase in the creatine excretion in these patients. Arginine, cystine, glutamic acid, histidine, nucleic acid and various other compounds had no such effect.

It is well known that the administration of benzoic acid results in a loss of glycine from the body, owing to the excretion of a combination of the benzoic acid with the glycine in the form of hippuric acid. This fact was utilized to determine the effect of such losses of glycine on the creatine excretion in our cases. It was repeatedly found that the administration of benzoic acid produced a prompt and appreciable decrease in the creatinuria[16].

The following is a list of the compounds investigated.

COMPOUNDS STUDIED IN MUSCULAR DYSTROPHY

Glycine	Urea
Guanido acetic acid	Uric acid
Sarcosine	Creatinine
i-Alanine	Creatine
d-Glutamic acid	Isocreatine
d-Arginine	Betaine
l-Histidine	Nucleic acid
l-Cystine	Edestin
Cysteine	Gelatin
i-Serine	Casein
l-Tyrosine	Ammonium acetate
d-Arginine and glycine	Ammonium chloride
Glycine and d-Glutamic acid	Benzoic acid
Glycine and l-Cystine	Phenylacetic acid
Glycine, d-Glutamic acid and l- Cystine	Ephedrine
Glycyl-Glycine	
Glucose	
Lactic acid	

Since, as already stated, the feeding of glutamic acid produced no effect on the creatinuria, it was considered desirable to investigate what effect the withdrawal of glutamic acid would have on the creatine excretion. This was accomplished by feeding phenylacetic acid, which, in man, is known to be excreted in combination with glutamine as phenylacetylglutamine. It was found[7,17] that such feeding had no effect on the level of creatine excretion.

We are inclined to infer from these 5 experiments that the feeding of brombenzene which removes cysteine from the metabolic mixture would be without effect on creatine excretion, since cystine did not give a rise in creatine excretion. Brombenzene is probably rather toxic so that we have not carried out such experiments on patients.

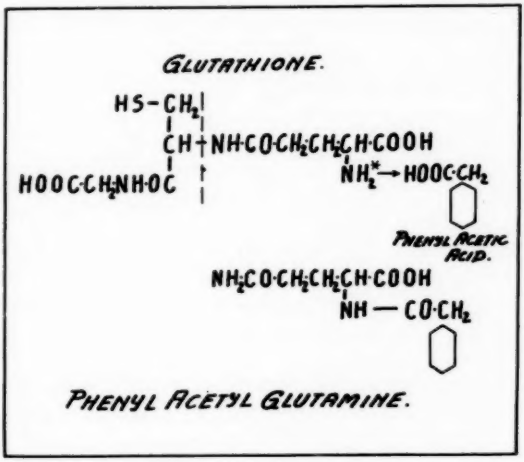
We have been led to believe from our experiments[7,17] that glycine, glutamic acid and cystine are probably present

in the metabolic mixture, although not as free amino acids as tissue analyses indicate, but in some combined form. In glutathione which is present in the body in large amounts we have such a combination. Now it is an interesting fact as Waelsch[18] and also Power[19] have pointed out, that the three amino acids—glycine, glutamic acid and cysteine which are the only three amino acids known to play a role in processes of detoxification are exactly those one finds in the molecule of glutathione.

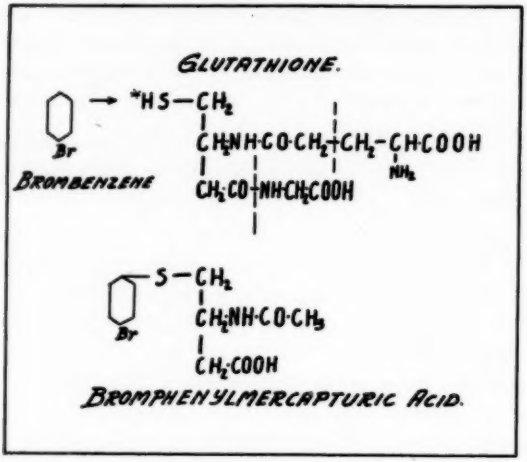
Since the feeding of benzoic acid markedly reduces creatine excretion in the cases of muscular dystrophy and if the glycine used to detoxify this substance comes from glutathione, then it would appear very possible that glycine plays its role in creatine metabolism via glutathione.

It may be interesting at this point to indicate the possible manner in which glutathione detoxifies phenylacetic acid and brombenzene.

E.g., phenylacetic acid would combine with α-amino group of the glutamic acid radical of glutathione (indicated by * in the formula), following which the side chain splits off completely at the α-carbon of the cysteine liberating phenylacetylglutamine.



Brombenzene would combine with the SH group of glutathione (indicated by * in the formula), following which the glycine is split off and *B*-oxidation takes place on the center carbon atom of the glutamic acid radical. Thus the acetyl group of bromphenyl mercapturic acid would be a remnant of the glutamic acid radical of glutathione and not due to a special process of acetylation. It is interesting to note that glutathione in this way may yield, under conditions, two molecules of glycine[16].



In 1929 we had occasion to discuss some phases of our studies with Professor Karl Thomas at the International Physiological Congress in Boston and to show him our detailed protocols when he visited us in New York City following the meeting. On his return to Leipzig, he repeated some of his earlier experiments on the origin of creatine with his special compounds on patients with muscular dystrophy but with negative results.

However, on repeating the experiments with glycine he was glad to be able to confirm our findings. Because of this established relation of glycine to creatine he undertook the

problem of the possible therapeutic effect of glycine in muscular dystrophy from its prolonged oral administration. Thomas, Milhorat and Techner[20] reported that some patients with muscular dystrophy were markedly improved from such therapy.

In this connection, it may be of interest to point out that only one or two out of 11 cases of muscular dystrophy reported by Milhorat with case histories showed definite improvement upon glycine administration. It is worthy of note that in these two cases, before the experiment was started, the average daily excretion of creatine was only 0.02 and 0.03 gm. respectively on a creatine-free diet. Considering the fact that in these cases the disease had been present for 14 and 15 years and that it was associated with appreciable physical disabilities, the almost negligible degree of creatinuria would seem most unusual for progressive muscular dystrophy. This would lead one to suspect that the cases perhaps belong to a special clinical group which responds to glycine treatment.

In 1932, we extended our metabolic studies in the myopathies to the investigation of the therapeutic effects claimed to have been obtained from prolonged administration of glycine. This phase of the work [17, 21] was carried out at the Psychiatric Institute with the cooperation of the Research Committee of the Neurological Institute and especially that of Drs. E. G. Zabriskie and C. C. Hare, who gave us valuable opinions regarding the neurological status of the cases. The work was aided, in part, by a grant from the Chemical Foundation. Up to date we have carried out metabolic and therapeutic observations in 46 cases of progressive muscular dystrophy of various types and severity and in 24 cases of various neuromuscular conditions and also several cases of myasthenia gravis and Graves disease. None of our patients with muscular dystrophy, receiving glycine therapy have shown any striking improvement such as that reported by Thomas, Milhorat and Techner and by Kostakoff and Slauck[22].

Of course it would be difficult to ascertain whether any slight improvement had occurred which could not be readily detected owing to the lack of satisfactory methods for measuring such improvement. In a number of cases, the families were of the opinion that the children were more active as a result of the therapy. However, objectively, no notable change has been observed as yet. Some of the patients have been receiving glycine for a period of more than one year and with perhaps one exception, there has been no apparent marked progress of the disease. One case of muscular dystrophy in a male of 45 years of age, who has been receiving glycine and glycine plus ephedrine for about one year, reported that he feels stronger and measurement of his muscles indicated that there has probably been an increase in the size of the musculature around one of the shoulders, which he felt was definitely stronger.

Boothby[23] of the Mayo Clinic, feels that glycine increases the efficacy of ephedrine in the treatment of myasthenia gravis. From our small experience with such cases, we can confirm the efficacy of ephedrine in some of the patients. We are not ready, however, to express any opinion regarding the effect of glycine. The experience of Boothby[23] and Moersch[24] regarding the effect of glycine in muscular dystrophy, as expressed at the last meeting of the American Medical Association, is essentially similar to our own.

The administration of glycine in a larger group of cases of muscular dystrophy is being continued particularly in children at an early stage of the disease in an endeavor to determine the possible therapeutic effect of glycine on the course of the disease over a period of years. Such continued and prolonged studies are made necessary because of the usual slow progress of the disease. Therapy also along other lines is being investigated.

LIST OF FOOTNOTES

1. Garrod, A. E. *Inborn Errors of Metabolism*, 2nd edition, London, 1923.
2. Lewis, H. B., *Ann. Inter. Med.*, 1932, **6**, 183.
3. Brand, E., Harris, M. M., and Biloon, S., *J. Biol. Chem.*, 1930, **86**, 315.
4. Grant No. 181 and 302.
5. Jackson, R. W., and Block, R. J., *J. Biol. Chem.*, 1932, **98**, 465.
6. White, A., and Lewis, H. B., *J. Biol. Chem.*, 1932, **98**, 607.
7. Brand, E., and Harris, M. M., *Science*, 1933, **77**, 589.
8. The Muscular Dystrophies, editorial, *Lancet*, 1925, **2**, 1179.
9. Folin, O., *Am. J. Physiol.*, 1905, **13**, 117.
10. Klercker, K. O., *Biochem. Ztschr.*, 1907, **3**, 45.
11. Failey, C. F., and Brand, E., *J. Biol. Chem.*, 1933, **102**, 767.
12. Rosenthal, M., *Handbuch der Diagnostik und Therapie der Nervenkrankheiten*, Erlangen, 1870.
13. Spriggs, E. I., *Quart. J. Med.*, 1907, **1**, 63.
14. Levene, P. A., and Kristeller, L., *Am. J. Physiol.*, 1909, **24**, 45.
15. Gibson, R. B., and Martin, T. F., *J. Biol. Chem.*, 1921, **49**, 319.
16. a. Brand, E., Harris, M.M., Sandberg, M., and Ringer, A. I., *Am. J. Physiol.*, 1929, **90**, 296.
    b. Brand, E., Harris, M. M., and Lasker, M. W., *J. Biol Chem.*, 1930, **87**, IX.
    c. Brand, E., and Harris, M. M., *J. Biol. Chem.*, 1931, **92**, LIX.
    d. Brand, E., and Harris, M. M., *J. Biol. Chem.*, 1932, **97**, LXII.
    e. Brand, E., and Harris, M. M., *Arch. sc. biol.*, 1933, **18**, No. 1-4.
17. Harris, M. M., and Brand, E., *J. Am. Med. Asso.*, 1933, **101**, 1047.
18. Waelsch, H., *Arch. Exp. Path.*, 1930, **156**, 356.
19. Power, F. W., Washington Meeting, 1933, Am. Chem. Soc.
20. a. Thomas, K., Milhorat, A. T., and Techner, F., *Ztschr. f. physiol. Chem.*, 1932, **205**, 93; 1933, **214**, 121.
    b. Milhorat, A. T., *Deutsch. Arch. f. klin. Med.*, 1933, **174**, 487.
21. Brand, E., and Harris, M. M., *J. Biol. Chem.*, 1933, **100**, XX.
22. Kostakoff, S., and Slauck, A., *Deutsch. Arch. f. Klin. Med.*, 1933, **175**, 25.
23. Boothby, W. M., *J. Am. Med. Asso.*, 1934, **102**, 259.
24. Moersch, F. P., *J. Am. Med. Asso.*, 1934, **102**, 267.

GOUT*

LEOPOLD LICHTWITZ

A physician, fifty years of age, "with a large head, of a full, humid and lax habitus, of a luxurious and vigorous constitution with excellent vital stamina," as Sydenham portrayed him, or in the words of Garrod, a man "of robust and large body, large head, of a full and corpulent habitus, whose skin is covered with a thick rete mucosum,"—a man, as Cullen described him, "of choleric-sanguine temperament," or as Gairdner stated, "of great vigor and apparent health,"—a physician devoted to science and with a warm heart for his patients, full of the love of life, humanity, art, and progress, gifted with a sense of humor, returns home on a winter evening, from a gay dinner with his friends. Getting out of his car his right foot touches the ground and he feels an overpowering pain in the basal joint of the great toe. He is unable to walk. A sweat breaks out. He removes his hat to dry his forehead, revealing thick shaggy eyebrows and a full crown of wavy hair. A few minutes later the pain is gone and believing that he had made a misstep, he forgets the incident entirely. The doctor goes to bed, and as usual, quickly falls asleep. About two hours later, between one and two o'clock, he awakens with a terrible pain in the same joint. At once he examines the painful foot. He notices no redness or swelling but finds the cutaneous veins of the foot and leg strikingly full and tense. The doctor faces his first gouty attack, so incomparably described from personal experience by that Hippocrates of English medicine, Sydenham. I shall not repeat Sydenham's description. His treatise is a delight and belongs to those classics which form the background of medical education.

Every detail of the short story just related is typical and has been repeated countless times during the course of centuries. Age, somatic and psychic constitution, season

*Delivered October 27, 1933.

and circumstance are characteristic for the gouty diathesis and the gouty attack. This first attack establishes the existence of a chronic disease. For, actually, gout is always a chronic disease although the stage characterized by the explosive attack is generally called acute gout. The predisposition to attacks and other manifestations is, indeed, latent but ever present.

This first attack was precipitated by extraneous and accidental circumstances such as cold weather, a good dinner and wine. In the absence of these factors the attack would not have occurred on this particular night and perhaps never. Obviously internal conditions were ripe for and conducive to an attack. In other words, the doctor, even before the acute episode, was already gouty. We must ask, "Is there any possibility of recognizing gout before the attack?"

This question brings up the difficult matter of the gouty constitution and of latent gout. Widely divergent views exist. There are those who frequently make a diagnosis of gout and use the term in a very broad sense. On the other hand, there are others who go so far as to deny the existence of the disease. Osler found that gout was often unrecognized in this country and Pratt has drawn particular attention to the scepticism in the minds of many practitioners regarding the existence of the disease. At the present time the recognition of gout in latent or atypical form is little recognized. In Germany, France, America, and even in England—the home of gout—the number of those afflicted with the typical disease is constantly decreasing. That its incidence was decreasing was observed as early as 1881 by Charcot.

The waves in the frequency and character of diseases constitute a curious phenomenon. In gout this is especially striking. Personality and character color the gouty picture in a remarkable way. No disease has such a predilection for eminent men. Among those in our own profession—to name only a few—are Sydenham, Harvey,

Linné, Widal. Amongst the men in pure science are Leibnitz and Newton, and among the historical figures are found such men as Wallenstein, Condé, Fox, the two Pitts, and many others. Charcot said, "the most distinguished statesmen become victims of gout." This situation seems to be much changed. The type of person has changed. The pyknics have lost in numbers and more so in influence. In place of the straightforward, erect, unaffected, humorous and generally rather asthenic type we find the high strung, rather nervous, and essentially asthenic type of diplomat whose bodily and mental makeup has not the characteristics of the typical gouty constitution. One can see that the fate of mankind is close to the history of gout. Gairdner, having the two Pitts in mind, stated that the disease is sometimes a matter of national and imperial interest.

The relation of the clinical picture of gout to personality is more marked than in any other disease. In the words of Gairdner, "The minute features of gout are found as various as the individuals whom it assails. We hear the patient speak of "his" or "my" gout, as if they were things of quite distinct creation."

In the presence of the constitution described, gout becomes manifest in persons who eat and drink excessively, at 50 to 60 years of age, when bodily exercise is reduced. In a smaller number of cases gout occurs in the absence of evidence of this constitution and in spite of physical activity and moderation in habits.

The importance of moderation and exercise in relation to etiology, prophylaxis and therapy of gout was recognized by Hippocrates. In the older literature there are interesting examples given (Schenkius, Gairdner) of rich men living in luxury, ease and indulgence, who, on becoming poor, were freed from their gout because of a sparing diet and bodily exercise or laborious occupation. Even many and large chalkstones (tophi) covering the joints disappeared.

These simple factors, capable of so much influencing gout in a marked form, may certainly be expected to be still more significant in prophylaxis. But there will be no progress and accomplishment if we are unable to recognize the gouty constitution as well as the forerunners of the gouty attack, and can convince the future victims of the necessity of prophylaxis.

Some facts concerning this disease are made clear when we realize that heredity plays a greater role in this disease than in any other except migraine. An hereditary factor is at play in at least 50 per cent of the cases. According to William Roberts, 75 per cent come of gouty stock. In a case cited by Garrod and in one of my own cases, gout could be traced in the family as far back as 400 years. The stronger the hereditary factor the earlier in life does the disease become manifest. This is especially true, it seems, if gout is inherited from the mother. Rarely, however, does the disease begin in childhood or before the age of twenty. Women are much less frequently affected by gout, the ratio to men being 1 :7.

When investigating the constitutional and hereditary factors, the inquiry should not be limited to gout. In the family as well as in the personal histories of the gouty, very frequently are discovered migraine and various manifestations of the angiospastic diathesis: also asthma, spasmodic vomiting, urticaria, acute articular rheumatism, and arthritis without urate deposits. The fact that an individual may in youth suffer from acute articular rheumatism and later in life develop gout, was pointed out by Llewellyn. Recamier said, "Gout and migraine are sisters." When migraine disappears, gout appears. The latter fact is well illustrated by a remarkable case cited by Trousseau. It is also well known that asthma may alternate with gout and that a prolonged attack of gout may be terminated with the outbreak of an urticarial rash. Duckworth made the significant observation that daughters of gouty fathers frequently suffer from so-called chronic rheumatic arthritis. This association of gout with

other diseases has been overlooked by physicians because of the overestimation of the significance of uric acid.

The association of gout with other diseases is the basis of the French concept of "arthritism," which has resulted in the recognition of gout as a member of the great family of allergic diseases. The joints and especially the periarticular tissues are known to be sites of marked allergic sensitiveness. It is not surprising, therefore, that Heberden's nodules frequently develop in individuals predisposed to gout, migraine and asthma, and in daughters of gouty fathers (Lécorchè).

The older literature contains examples of gouty fits occurring after certain foods. It has also been known for a long time that a specific hypersensitiveness may exist for a certain alcoholic beverage, and thus give rise to attacks of gout. One person may have an idiosyncrasy to beer, another to champagne. Widal who was gouty himself and was the first to recognize the allergic nature of gout, noted a hypersensitiveness to a particular wine and came to the conclusion that the allergen was a protein substance formed from the yeast.

In gout as in all other conditions in which allergy plays a role, hypersensitiveness is not limited specifically to a single substance. It exists not only for exogenic substances such as those that are introduced with the food, but also for a number of substances which are developed in the body itself. Active substances of the latter type are formed in the tissues by mild or severe tissue damage, by contusions, operative manipulations, etc. They also develop under the influence of local cooling, as, for example, in cold, wet feet, and as a result of emotional disturbances and strenuous mental effort. All these factors play a role in the manifestations of gout and in determining the occurrence of the gouty attack. Thus Garrod remarked that a blow, a fall or injury frequently determines the localization of the attack. A letter from Sydenham to Dr. Short is illustrative of the influence of emotions and mental strain. In it Sydenham says, "By applying my mind to its

utmost and by bringing all my powers of thought on the subject (namely the subject gout) I brought on a fit of gout as I had never suffered from. Whenever I returned to my studies, gout returned to me." It is evident then, that gout is not only, as the older physicians asserted, a daughter of Venus and Bacchus, but that Pallas Athena has some part in the child.

Simulating other allergic diseases, the gouty attack, at least in a certain stage of the disease, occurs periodically, at regular intervals. As after other allergic attacks there is also following a gouty one, a period of well being. "The worse the pain, the shorter the fit; the shorter the fit the longer and more complete the intermission." (Sydenham). The attack seems to be in the nature of a purifying thunderstorm. It is in all probability correct to say that the attack results in desensitization.

Besides its connection with allergic disease gout is related to the formation of nephrolithiasis. Garrod wrote, "In later years gout develops when in early life gravel and calculi are formed." This opinion finds no corroboration in our time since kidney stones are so frequent and typical gout so uncommon. Unquestionably gout leads to the formation of stones in some instances and, indeed, not only urate but also oxalate stones.

The kidney in the gouty diathesis is inclined to the formation of urinary sediment. We are dealing with a kidney secretion of inferior value, demonstrating in itself the participation of the kidney in this diathesis. In gout as in the new born there are formed uric acid infarcts in the form of whitish streaks in the medullary substance, sometimes in the pyramids. This deposition of urates in the parenchyma as well as the formation of gravel and stones may be the cause of the hematuria which we frequently encounter in the gouty. This relation of renal calculi to gout led Erasmus to express himself in a letter to Thomas Moore, thus, "Thou hast gravel and I have gout. We have married two sisters."

Having investigated the constitutional and hereditary situation and having been either led to suspect or actually recognize a gouty predisposition in an individual, the question arises: Is there from this point until the first attack a completely uneventful hiatus, or are there symptoms, or signals, perhaps slightly noticeable, which give the clue to the experienced clinician? The answer is: Yes, there are prodromal symptoms which although in no way specific are significant because they are numerous.

The forerunners of the attack at first involve the organs of digestion. Dyspepsia, capricious appetite, gastric acidity, pyrosis, constipation, and attacks of sudden painful diarrhea, mostly at night, occur. The tongue is heavily coated, red at the tip and edges, and there is a disagreeable taste in the mouth. After meals there is a feeling of distension in the epigastrium, a fullness over the hepatic region and a slight swelling of the liver. Enlargement of the liver occurs normally during the hours of digestion but not to the degree to which it does in this stage of developing gout. This enlargement is the result of contraction of the hepatic veins. We know that this contracting apparatus is subject to allergic sensitivity and shows its greatest reaction in anaphylactic shock. It is therefore permissible to presume that allergic sensitivity plays a role in the enlargement of the liver in gout.

Another prodromal symptom is the reduction of urinary output, occurring from time to time, not noticeable most of the time, yet occasionally expressing itself as visible swelling of the hands. A tendency to edema, and edema proper, may be of allergic origin. There are other cutaneous manifestations. Gairdner notes that an unnatural dryness of the skin may precede the attack by months and even years. Sweat and sebaceous exudation of the armpits and toes disappear. These parts become hot and itching. The most common conditions are urticaria, psoriasis, eczema, especially dry eczema of the eyebrows. Pains in muscles and joints appear as abrupt twinges. Great tenderness of the feet develops while walk-

ing but may also occur while the patient is at rest or is lying in bed. The gouty may complain of tenderness, stiffness and a feeling of shortness in the tendo Achilles. Graves has emphasized the occurrence of sudden pains or twitches which last only for a few minutes or even seconds. Gairdner speaks of "a dull pain in the left side of the chest, pain, pricking and tenderness in the ears or at the side of the finger joints, pain in the eyeballs or in the lumbar regions and sciatica." He also draws attention to cramps of the muscles occurring at night or when walking.

The older physicians spoke of asthma, coughing, heartburn, oppression, and irregularities of the heart as forerunners of the attack. Today we are more reserved in the evaluation of these symptoms. We are, however, definitely certain of changes in the character and disposition as being forerunners of manifest gout. Lassitude, prostration, sleeping after food, interrupted sleep at night, are such symptoms. The person becomes hypochondriacal, morose, irritable and unable to perform any kind of intellectual labor. There are explosive mental outbursts. The irrascibility of the gouty is proverbial.

These symptoms are not of themselves characteristic. Yet they belong to gout. This is verified by the common observation that symptoms peculiar to the individual precede each attack for many years and that the patient who has not forgotten his first attack together with its prodromata can sense the approach of the next. His family and associates who have put up with this change in character and manners can similarly predict the visit of an attack.

It is the prodromal period which is the best time for treatment. But because of his confidence in his vitality and vigor, his unconscious conviction of his right to invulnerable health, both inherent in the very character of the gouty man, this causes him in most cases to neglect and suffer the forerunning symptoms and to refuse the advice of his wife and physician. The painful experiences of even many attacks will often not suffice to convince a

gouty person to change his mode of life. Thus the incurability of gout and its tendency to progress have their foundation in the gouty constitution proper.

Before an attack the prodromal symptoms increase but sometimes disappear to give way to an abnormal sense of well being which is in turn abruptly terminated by the attack.

Gout appears in various forms. We have spoken of acute and chronic gout. The terms regular, irregular, atonic and visceral gout have been in use for a long time. The older clinicians designated as retrocedent gout those diseases of the internal organs which made their appearance during an attack or at its sudden termination. Cerebral apoplexy and cardiac disturbances, when they occurred in an individual afflicted with gout, were labeled gouty.

The form in which gout appears is dependent upon the individual constitution. The manner in which gout changes in the course of years depends upon the changes in the individual brought about by the illness and advancing years.

The most satisfactory bird's eye view of the disease is given by Gairdner who divides the disease into three stages.

1. Attacks at regular or irregular and distant intervals. Unhurt constitution. Severe fits, but afterwards the patient feels little inconvenience and forgets his misfortune.

2. The fits are seldom as painful as in its earlier period, but frequent. Diminished strength. The step has lost its elasticity, the head its firmness and resolution, the handwriting becomes tremulous and indistinct. Any excess makes inconvenience (dyspepsia). Enlarged subcutaneous veins appear over the face. The eyes become bleared. Conjunctivae become filled with blood. The patient represents an altered being.

3. Melancholy stage. Rarely decided attack, but the malady is never absent. In summer there is a short intermission of suffering. Indigestion, muscular and nervous weakness, heart trouble.

Not every patient passes through these three stages. If gout affects an individual who does not possess the gouty constitution but is of asthenic type with muscular weakness and of a nervous temperament, the disease will express itself as atonic or irregular gout in the third stage.

The most certain of the diagnostic criteria of gout is the tophus. Tophi may appear before the first attack and are especially easy to recognize when situated at the margin of the ear (helix). They develop painlessly and are usually unnoticed. In its first stage the tophus is neither hard nor white but soft and apparently fluid in consistency. The skin covering it is unchanged. It is important to point out that the tophus does not develop as the result of inflammation. It gains its characteristic shape by filling with crystalline urate and by the thinning of the overlying skin. The formation and disappearance of tophi is independent of the occurrence of attacks. They are not tender—they do not show urates in every case, but always necrosis of tissue. According to the view of Ebstein, which I consider to be the correct one, though it be contrary to that of most pathologists, the tissue damage which ultimately leads to necrosis is the primary process. This tissue injury is not caused by the uric acid for the latter is not a toxin and is incapable of injuring tissues, as a study of uric acid infarcts in the new born readily discloses.

Since the time of Garrod the view that uric acid is a poison and is the toxin of gout has been firmly rooted in the minds of most physicians. There is no evidence for this view. Birds and reptiles form great quantities of uric acid from urea. It would be contrary to the wisdom of nature to form a toxic substance from a non-toxic one such as urea.

In gout uric acid is apparently retained in the body. This is attested to by the fact that hyperuricemia is demonstrable not always but in the majority of instances. Garrod was the first to suggest that a damage to the kidney was responsible for this retention. Later on this damage was expressed as a disturbance in the partial function of concentration of urate (Lichtwitz, Thannhauser) as it occurs in renal disease. Thus some patients with diseased kidneys show hyperuricemia and urate deposits but fail to give any evidence of gout.

Hyperuricemia and the gouty attack have no recognizable relationship. This is supported by many examples. I refer only to a few.

A very prominent physician who had previously suffered from severe attacks of gout is now free of them though his blood uric acid is 16 mgm. per cent. A patient at the Montefiore Hospital, gouty, with a tophus in his ear, has been free of attacks for a long time although his blood uric acid has ranged between 9.2 to 14.8 mgm. per cent. We have recently observed a 54 year old man with gout and calculi in his kidney, and saw him in typical colics with a blood urate of 6-7 mgm. per cent. Several weeks after an attack the patient became anuric as a result of ureteral obstruction by a calculus. His uricemia rose to 24 mgm. per cent but no attack occurred. On the other hand, it is well known that attacks may occur in the presence of a normal and even a subnormal uric acid content of the blood.

Sometimes tophi break through the skin, and chalk-like masses are evacuated which contain numerous crystalline needles of sodium biurate (Demonstration). It seems very peculiar that these skin wounds never become infected.

As mentioned above the first visible change in a gouty attack is local venous stasis, a phenomenon described by the older clinicians and noted in every instance by myself. Later the swelling appears and with its appearance the pain decreases. It seems, corresponding to Gairdner's

suggestion, that the attack begins with a peculiar local disturbance of the circulation affecting veins and capillaries. This may be the basis for the occurrence of gouty phlebitis as first described by Sir James Paget, and of ecchymosis in the skin covering the diseased joint.

In 70 per cent of the cases the first attack involves the basal joint of the great toe, which is exposed to the largest load and greatest pressure. A part which had previously been injured is certain to be the seat of the gouty inflammation in subsequent attacks.

In serious cases the disease is widespread, involving many joints, the muscles, cartilages, tendons and internal organs. In such cases one finds tophi in the cartilages of the nose, in the eyelids, auditory ossicles (Harvey), corpora cavernosa (priapism), atheromatous aorta and in the walls of the bronchi. Finally, in the words of Sydenham, "the whole body is converted into a tophus."

Many of the details of the gouty picture such as the ocular affections, the urethritis, the bone and joint destruction with its anatomic and roentgenographic features, and many others, cannot be considered tonight.

We come, finally, to a consideration of therapy.

Today, as in the time of Hippocrates, moderation and exercise are the most important factors in treatment.

Concerning dietary therapy one may say that the purine free diet stands much higher in the estimation of physicians than of the patients suffering from gout, and I might add, that their judgment deserves more consideration than that of other patients. Llewellyn makes the pointed remark, "The purine free diet smacks too much of the laboratory." It should only be ordered as a cure of limited duration for 4 to 6 weeks in the form of a raw food diet or as a grapecure. The individuality of the patient must be taken into consideration. A muscular and plethoric young man cannot be given the same diet as a weak old person with atonic gout. Limitation of food to a maintenance

level is much more important than elimination of the purine containing foods. Ebstein states that the gouty who have grown old in spite of their disease are almost always those who have been able to avoid obesity. Diet in general should be suited to the individual and the disease. Its preparation should be as simple as possible. A diet with limitation to one dish of meat or fish per day given only on 5 or 6 days per week is sufficient curtailment and is followed more rigorously by patients than the purine free diet. There is no need for the general prohibition of alcoholic beverages. I agree with Llewellyn that total abstinence is not prudent in middle or late life. Total abstainers are not exempt from gout. Which drinks are to be permitted depends upon the allergic sensitiveness of the individual. The latter information can usually be obtained from a study of the history.

During the attack rest is prescribed. Local applications, warm or cold, according to the patient's desire, should be applied. Cinchophen may be given in doses of 3 grams per day but for not longer than four successive days. This should be given together with a large amount of water or tea. Sodium salicylate 3-6 grams per day, if necessary by enema, is less harmful and nearly equally efficient.

The only specific against the gouty attack is colchicum. It should never be given, however, at the beginning of an attack and never to weakened individuals. Colchicum is in bad repute among many of the gouty, the reason being that when administered in high doses, as not infrequently happens there may ensue diarrhea, weakness and collapse. Gairdner in his remarks on therapy says, "Colchicum never more effectually relieves the patient than when it acts silently and peacefully, without producing any evacuation whatever or in any way disturbing the patient's comfort and ease." Experienced gouty patients advise that colchicum is best taken in the morning hours in ½ mgm. doses, three or four times during the first day, doubling the dose on the succeeding two or three days. It is re-

duced in quantity or entirely stopped when diarrhea appears or any other disturbance is manifested.

Colchicum exercises its pharmacologic effect on the capillaries and periarticular tissues, being capable in high dosage of causing arthritic attacks. This is of significance and is in harmony with the viewpoint that the gouty attack is an allergic reaction involving veins, capillaries and joints.

Nothing can be more unwise for the patient, than immediately after a cure of gout by this means to revert to the usual course of life. In the period after and between attacks the regulation of the mode of life is of prime importance. During this time, I believe, it is useful to put the patient on lemons and administer ½ to 1 teaspoonful of washed sulphur in water at night.

Sydenham concludes his famous dissertation on gout as follows: "As for a radical cure, this lies like Truth, at the bottom of a well; and so deep is it in the innermost recess of Nature that I know not when or by whom it will be brought forward into the light of day." These words still ring true today.

LIBRARY HOURS DURING THE SUMMER

As usual, the Library will be closed daily at 5 P. M. instead of 10:30 P. M., Wednesdays excepted, from June 15th to September 15th, inclusive. It will be open only on Wednesday evenings until 10:30 P. M.

THE LINSLY R. WILLIAMS MEMORIAL MEETING

To do honor to his memory, Fellows of the Academy and friends of Dr. Linsly R. Williams, gathered in Hosack Hall on April 26, 1934, to participate in a memorial meeting.

Dr. Bernard Sachs opened the meeting, and both as President of the Academy and as a devoted friend to Dr. Williams, pointed to the gathering as evidence of the deep affection in which he was held and the loss which was felt by the Fellowship of the Academy in the death of its first Director.

The program of the meeting included three addresses dealing with various aspects of Dr. Williams' life.

Dr. John H. Finley spoke on Dr. Williams as a Citizen. With the text taken from the Religio Medici of Sir Thomas Browne, "There is a nobility without heraldry, natural dignity, whereby one man is ranked with another, another filed before him, according to the quality of his desert and preeminence of his good parts," Dr. Finley dwelt upon the person and services of Dr. Williams. "His head ever moved a little before his square shoulders as if ever inquiring the way of advance and ready for anything. But seeing his eyes, one could never mistake him for another — the gentleness of their salutation, the depth of understanding which they revealed, the quiet determination and their preparation against any surprise . . . Linsly Williams died a man, who lived up to its high definition — a man 'beloved and elect of men.' "

Dr. Livingston Farrand dealt with Dr. Williams' Contribution to Public Health and Medicine, beginning with Dr. Williams' entrance upon the practice of medicine in New York and his participation in the Metropolitan Sewage Commission organized in 1908. The subsequent phases of his public health career were briefly touched on by Dr. Farrand, his review culminating in Dr. Williams' assumption of the Directorship of the New York Academy of Medicine in 1924.

Of the qualities of his character which made Dr. Williams so eminently fruitful in his services to public health and medicine, Dr. Farrand said, "Many qualities were joined to make that life unusual. Natural quickness of perception, trained through years of experience, gave a background for the development of that soundness of judgment and that sagacity in affairs that in Dr. Williams' maturer years were demonstrated so often and were so widely recognized. A singularly winning personality eased the approach to any necessary discussion of a situation and an obviously disinterested attitude disarmed the skepticism of even the politically minded. A sense of humor, always valuable in forming judgments and usually dangerous in public expression, was held in check—sometimes it is true with difficulty. A healthy interest in any person or any event of significance in history or contemporary life constantly enriched the store of knowledge against which he placed any new problem for comparison and solution. And all these qualities and gifts were shot through with an idealism that was invariably present even though seldom voiced."

Dr. John A. Hartwell spoke on Dr. Williams as a Friend of the New York Academy of Medicine and its Fellows. Dr. Hartwell reviewed the history of the events which led up to the assumption of the Directorship of the Academy by Dr. Linsly R. Williams. He made special reference to the breadth of vision and tenacity of purpose which inspired a group of Academy Fellows, among whom were Delavan, Thompson, James and Stewart, to extend the influence and deepen the effectiveness of the Academy. To this "noteworthy conjunction of events" there was added the happy and wise influence of a generous benefactor, whose benevolence to the Academy was conditioned on the assumption of the direction of the affairs of the Academy by a man properly trained and fitted for the task. With what energy, intelligence and fidelity Dr. Williams assumed and exercised his office was the major substance of Dr. Hartwell's address.

To the concluding words of Dr. Hartwell, in which there was an exhortation and a pledge: "Let us dedicate ourselves to the task of realizing his ideals and let us keep the name of Linsly Rudd Williams as a symbol of doing for others and making life a sweeter, better and happier experience," the audience gave full hearted assent by standing for a minute in silent tribute.

The Linsly R. Williams Memorial Meeting was arranged by a special subcommittee, who are also charged with the publication of the Linsly R. Williams Memorial Volume, in which will appear the addresses delivered at the memorial meeting, as well as other pertinent material bearing on the life of Dr. Williams.

PROCEEDINGS OF ACADEMY MEETINGS MARCH and APRIL

STATED MEETINGS
March 1

I. EXECUTIVE SESSION—a. Reading of the Minutes; b. Election of Benefactor; c. Election of Officers; d. Election of Fellows and Members; e. Vote on Constitution and By-Laws.

II. PAPERS OF THE EVENING—SYMPOSIUM: THE PROBLEM OF CAVITATION IN PULMONARY TUBERCULOSIS—a. From the medical standpoint, Edgar Mayer; b. From the surgical standpoint, Edward S. Welles, Saranac Lake; c. The roentgenological differential diagnosis of the tuberculous cavity, Ross Golden; d. Discussion, J. Burns Amberson, Jr.

THE HARVEY SOCIETY (IN AFFILIATION WITH THE NEW YORK ACADEMY OF MEDICINE)
March 15

THE SIXTH HARVEY LECTURE, "The Significance of Morbid Process in the Fetus," George L. Streeter, Director, Department of Embryology, Carnegie Institute of Washington, Baltimore.

SECTION MEETINGS

SECTION OF SURGERY—March 2

I. PRESENTATION OF CASES—a. 1. Obstructive jaundice, Choledochoduodenostomy; 2. Acute osteomyelitis of the tibia; 3. Osteochrondroma of the femur, Gaston A. Carlucci; b. 1. Recurrent fibroma—five-year result, Paul C. Morton; c. Two cases illustrating paper, Charles W. Lester; d. One case illustrating paper, James R. Lincoln.

II. PAPERS OF THE EVENING—a. Fractures of the odontoid process of the second cervical vertebra, James R. Lincoln; b. Chronic appendicitis and the right lower quadrant syndrome, Charles W. Lester.

III. GENERAL DISCUSSION—Clay Ray Murray, Byron Stookey, Frederic W. Bancroft, Wm. Crawford White.

IV. EXECUTIVE SESSION—Appointment of Nominating Committee.

SECTION OF DERMATOLOGY AND SYPHILOLOGY—March 6

I. PRESENTATION OF CASES FROM CITY HOSPITAL.

II. PRESENTATION OF MISCELLANEOUS CASES.

III. DISCUSSION OF SELECTED CASES.

IV. EXECUTIVE SESSION—Appointment of Nominating Committee.

JOINT MEETING—SECTION OF NEUROLOGY AND PSYCHIATRY and THE NEW YORK NEUROLOGICAL SOCIETY—March 6

I. READING OF THE MINUTES.

II. PRESENTATION OF NEUROLOGICAL CASES OF UNUSUAL INTEREST.

III. GENERAL DISCUSSION.

IV. EXECUTIVE SESSION OF THE SECTION—Appointment of Nominating Committee.

JOINT MEETING UNDER THE AUSPICES OF THE NEW YORK ACADEMY OF MEDICINE, NEW YORK OBSTETRICAL SOCIETY and THE MEDICAL SOCIETY OF THE COUNTY OF NEW YORK

March 7

at The New York Academy of Medicine, 2 East 103rd Street

CONSTRUCTIVE ASPECTS OF THE ACADEMY OF MEDICINE REPORT ON MATERNAL MORTALITY—1. Resume of the Report, Harry Aranow; 2. Conclusions and Recommendations of the Report, George L. Brodhead; 3. Significance of the Report and the Measures Suggested for Carrying Out its Recommendations, George W. Kosmak. DISCUSSION—A. W. Bingham, East Orange, New Jersey; Clifford B. Lull, Philadelphia; Edward C. Podvin, New York City; S. S. Goldwater, Commissioner of Hospitals; John L. Rice, Commissioner of Health, and Thomas L. Parran, State Commissioner of Health.

COMBINED MEETING OF THE SECTION OF PEDIATRICS and the SECTION OF OBSTETRICS AND GYNECOLOGY—March 8

I. EXECUTIVE SESSION—Appointment of Nominating Committee.

II. PAPERS OF THE EVENING—a. Morphinism in the new-born—A case report, R. Gordon Douglas (by invitation); b. Gas therapy in obstetrics and pediatrics, Paluel J. Flagg (by invitation). Discussed by Richard N. Pierson. c. Natimortality, Hugo Ehrenfest, St. Louis (by invitation). Discussed by William E. Studdiford.

III. GENERAL DISCUSSION.

SECTION OF HISTORICAL AND CULTURAL MEDICINE—March 14

I. READING OF THE MINUTES.

II. PAPERS OF THE EVENING—a. How the President, Thomas Jefferson, and Dr. Benjamin Waterhouse established vaccination as a public health procedure (with exhibit), Robert H. Halsey; b. Medicine among the American Indians (with lantern slides), Eric Stone, Providence, R. I. (by invitation).

III. GENERAL DISCUSSION.

IV. EXECUTIVE SESSION—Report of Nominating Committee.

SECTION OF ORTHOPEDIC SURGERY—March 16

I. READING OF THE MINUTES.

II. PRESENTATION OF CASES—a. Cineplastic amputation—case reports, Henry K. Kessler (by invitation); b. Sacroiliac strain secondary to lumbo-sacral fusion, Lewis C. Wagner; c. Living suture repair of fractures about the patella, Charles M. Gratz (by invitation).

III. PAPERS OF THE EVENING—a. Vital capacity in spinal deformities, Kristian G. Hansson (by invitation); b. End results in the treatment of slipping of the upper femoral epiphysis, Maurice M. Pomeranz, Marian Frauenthal Sloane (by invitation).

IV. DISCUSSION—Samuel Kleinberg, Armitage Whitman, Harry Finkelstein, Leo Mayer.

V. EXECUTIVE SESSION—Appointment of Nominating Committee.

SECTION OF OPHTHALMOLOGY—March 19

I. INSTRUCTION HOUR—7 to 8 o'clock—Ophthalmoscopy—lantern slides, Arthur J. Bedell.

II. DEMONSTRATION HOUR—7:30 to 8:30 o'clock—a. Cases with divergence muscle anomalies; b. Ophthalmotrope, Wendell L. Hughes; c. Instruments used for testing muscle anomalies.

III. SECTION MEETING—8:30 to 10:30 o'clock—a. Executive Session; 1 Reading of minutes; 2. Appointment of Nominating Committee; b. Scientific Paper; 1. Divergence excess, Arthur Bielschowsky (by invitation). Discussers: 1. Herbert W. Wootton; 2. P. Chalmers Jameson (by invitation); 3. James W. White; 4. John H. Dunnington; 5. Le Grand H. Hardy.

SECTION OF MEDICINE—March 20

I. READING OF THE MINUTES.

II. PAPERS OF THE EVENING—a. Further studies of the effect of tobacco on the peripheral vascular system, Irving Sherwood Wright, Dean Moffatt (by invitation); b. Insufficiently appreciated conceptions in the relation of the thyroid gland to Graves' disease, Henry B. Richardson; c. Clinical considerations concerning the detoxifying function of the liver, Armand J. Quick (by invitation); d. A case of diabetes of unusual type of insulin resistance, Bertram J. Sanger (by invitation) Henry E. Marks (by invitation); e. An epidemic (21 autopsies) of aestivoautumnal malaria in drug addicts transmitted by hypodermic syringe, Milton Helpern (by invitation).

III. GENERAL DISCUSSION.

IV. EXECUTIVE SESSION—Appointment of Nominating Committee.

SECTION OF GENITO-URINARY SURGERY—March 21

I. READING OF THE MINUTES.

II. PRESENTATION OF INSTRUMENT—A new female urethroscope, Paul M. Butterfield.

III. PAPERS OF THE EVENING—a. Calculous anuria, George F. Cahill; b. Some ureteral problems, John R. Caulk, St. Louis (by invitation). Discussion: Edwin Beer, Harold H. Gile (by invitation), Edward L. Keyes, Nathaniel P. Rathbun.

IV. GENERAL DISCUSSION.

V. EXECUTIVE SESSION—Appointment of Nominating Committee.

SECTION OF OTOLARYNGOLOGY—March 21

I. READING OF THE MINUTES.

II. APPOINTMENT OF NOMINATING COMMITTEE.

III. CASE PRESENTATIONS—a. Prickle cell epithelioma of the ear with involvement of the facial nerve, Ward C. Denison. Discussion: T. J. Harris. b. Otitic hydrocephalus, Clarence H. Smith. Discussion: S. P. Goodhart.

IV. PAPERS OF THE EVENING—a. The window operation for hematoma auris and perichrondritis with effusion, Robert C. Howard. Discussion: Ralph Almour, J. Coleman Seal. b. Avulsion of the vocal cord, John M. Loré. Discussion: David H. Jones, Charles J. Imperatori, M. C. Myerson, L. Glushak, E. Josephson. c. A simple surgical method of dealing with calculi in the submaxillary salivary duct, August L. Beck. Discussion: Lee M. Hurd, Theodor Blum.

V. GENERAL DISCUSSION.

AFFILIATED SOCIETIES

NEW YORK ROENTGEN SOCIETY IN AFFILIATION WITH THE NEW YORK ACADEMY OF MEDICINE
March 19

I. 8:00 to 8:30 p.m.—Demonstration and discussion of interesting cases.

II. 8:30 p.m.—Bone changes in cases of disturbance in lipoid metabolism, Leopold Jaches.

NEW YORK MEETING OF THE SOCIETY FOR EXPERIMENTAL BIOLOGY AND MEDICINE UNDER THE AUSPICES OF THE NEW YORK ACADEMY OF MEDICINE—March 21

I. *In vivo* and *in vitro* cultivation of the virus of rift valley fever, R. S. Saddington (Read by T. M. Rivers).

II. Distribution of virus of louping-ill in blood and brain of intranasally infected mice, G. L. Fite, L. T. Webster.

III. Ultra-filtration experiments with the encephalitis virus from the St. Louis epidemic, J. H. Bauer, G. L. Fite, L. T. Webster.

IV. Formation of agglutinins with lymph nodes, P. D. McMaster, S. S. Hudack.

V. Reaction of the rabbit to vaccine virus, L. Pearce, P. D. Rosahn, C. K. Hu.

VI. Differential ovarian responses after injections of follicle-stimulating and pregnancy urine in young female rats, P. E. Smith, E. T. Engle, H. H. Tyndale.

VII. Gametokinetic action of extracts of follicle-stimulating urine, P. E. Smith, E. T. Engle, H. H. Tyndale.

VIII. Action of pregnancy urine extract (Follutein) on external genitalia of female guinea pigs, G. N. Papanicolaou, E. A. Falk.

IX. Inversion of the P wave in the third lead of electrocardiograms with a large Q-3 wave, C. Shookhoff, A. H. Douglas (Introduced by H. Gold).

NEW YORK PATHOLOGICAL SOCIETY IN AFFILIATION WITH THE NEW YORK ACADEMY OF MEDICINE—March 22

I. PRESENTATION OF CASES.

II. PAPERS OF THE EVENING—a. Dilatation of the pulmonary artery; 1. Idiopathic; 2. Associated with cardiac anomalies, B. S. Oppenheimer; b. Pathology of measles with special reference to pneumonia, L. W. Smith; c. A review of recent studies of yellow fever, W. A. Sawyer (by invitation).

STATED MEETINGS

Program arranged in cooperation with the New York Pathological Society.
April 5

I. EXECUTIVE SESSION—a. Reading of the Minutes; b. Election of Fellows and Members.

II. PAPERS OF THE EVENING—SYMPOSIUM: RECENT PROGRESS IN LEUKEMIA RESEARCH; a. Experimental aspects, Maurice N. Richter (20 min.), Jacob Furth (20 min.); b. Pathology, Richard H. Jaffe, Chicago (30 min.); c. Clinical and therapeutic aspects, Lloyd F. Craver (20 min.); d. Discussion, Francis C. Wood, Nathan Rosenthal.

THE HARVEY SOCIETY (IN AFFILIATION WITH THE NEW YORK ACADEMY OF MEDICINE)
April 19

THE SEVENTH HARVEY LECTURE, "Filtrable Viruses with Particular Reference to Psittacosis," Thomas M. Rivers, Member of the Rockefeller Institute.

SECTION MEETINGS

SECTION OF DERMATOLOGY AND SYPHILOLOGY—April 3

I. PRESENTATION OF CASES FROM—Beth-Israel Hospital, Seaview Hospital.

II. PRESENTATION OF MISCELLANEOUS CASES.

III. DISCUSSION OF SELECTED CASES.

IV. EXECUTIVE SESSION.

V. NOMINATION OF SECTION OFFICERS AND ONE MEMBER OF ADVISORY COMMITTEE.

JOINT MEETING SECTION OF NEUROLOGY AND PSYCHIATRY and the SECTION OF DERMATOLOGY AND SYPHILOLOGY—April 10

I. READING OF THE MINUTES.

II. PAPERS OF THE EVENING—a. Psychogenic aspects of skin diseases, Joseph Klauder; b. Remarks on the psycho-physiology of the skin, Paul Schilder.

III. DISCUSSION—Charles M. Williams, Abraham Walzer, Smith Ely Jelliffe, J. Ramsay Hunt.

IV. EXECUTIVE SESSION OF THE SECTION OF NEUROLOGY AND PSYCHIATRY—Nomination of officers and two members of the Advisory Committee.

COMBINED MEETING OF THE SECTION OF PEDIATRICS AND THE SECTION OF SURGERY—April 12

I. EXECUTIVE SESSION—Nomination of Section Officers and One Member of Advisory Committee.

II. PAPERS OF THE EVENING—a. Two cases of pneumococcus peritonitis, John V. Bohrer; b. One case of pneumococcus peritonitis, Philip D. Allen; c. Pneumococcus peritonitis from the pediatric viewpoint, Murray H. Bass; d. Pneumococcus peritonitis from the surgical viewpoint, Edward Donovan; e. Pneumococcus peritonitis in nephrosis, John D. Lyttle. Discussion: Harold Neuhof, Bernard Denzer, William Heeks (by invitation).

SECTION OF OPHTHALMOLOGY—Monday Afternoon and Evening, April 16

I. Demonstration of the mechanism and use of the ophthalmo-Eikonometer, an instrument for determining Aniseikonia (i. e., differences in the size and shape of ocular images), 3 to 5 o'clock.

II. INSTRUCTION HOUR, 7 to 8 o'clock—A new method of microanatomy of the eye; 1. Comparative anatomy of the angle of the anterior chamber in living and dead eyes, Manuel Uribe Troncoso (by invitation), Ramon Castroviejo (by invitation).

III. Demonstration of patients corrected for aniseikonic defects, 7:30 to 8:15 o'clock—Slit Lamp Studies, Milton L. Berliner, Isadore Goldstein, Wendell L. Hughes, Girolamo Bonaccolto (by invitation).

IV. PAPERS OF THE EVENING, 8:15 to 10 o'clock—a. The nature of fixation and its effect on the physiology of visual acuity, Francis H. Adler (by invitation); b. Aniseikonia—Differences in size and shape of ocular images, Mr. Julius Neumueller, B.S., O.D. (by invitation); c. Examination and treatment of aniseikonia, Mr. Leo F. Madigan (by invitation). Discussion: Elmer H. Carleton (by invitation), Wendell L. Hughes, Mr. Adelbert Ames, Jr. (by invitation).

V. EXECUTIVE SESSION—Reading of the Minutes; Nomination of Section Officers and one member of Advisory Committee.

COMBINED MEETING OF THE SECTION OF GENITO-URINARY SURGERY and the SECTION OF MEDICINE—April 18

I. READING OF THE MINUTES.

II. PAPERS OF THE EVENING—PERINEPHRITIS AND PERINEPHRITIC ABSCESS; 1. From the Medical standpoint, Henry B. Richardson; 2. From the urologic standpoint, Henry G. Bugbee. Discussion to be opened by Nathaniel P. Rathbun.

III. GENERAL DISCUSSION.

IV. EXECUTIVE SESSION—Section of Medicine, Nomination of Section officers and one member of the Advisory Committee; Section of Genito-Urinary Surgery, Nomination and election of Section officers and one member of the Advisory Committee; *No May Meeting of this Section will be held.*

SECTION OF OTOLARYNGOLOGY—April 18

I. READING OF THE MINUTES.

II. EXECUTIVE SESSION—Nomination of Section officers and one member of Advisory Committee.

III. CASE PRESENTATIONS—a. Presentation of patients with laryngeal carcinoma treated by roentgen rays, I. Seth Hirsch. Discussion: Ira I. Kaplan, Maurice Lenz. b. A case of myoblastoma of the larynx, Louis Kleinfeld. Discussion: Paul Klemperer.

IV. PAPERS OF THE EVENING—a. Roentgenologic interpretation of cysts and tumors of the upper jaw, S. Fineman. Discussion: P. Klemperer. b. Cancer of the larynx; some conclusions derived from personal experience, Joseph C. Beck (by invitation), M. Reese Guttman, Chicago (by invitation). Discussion opened by: Caesar Hirsch, formerly medical director, nose and throat service, Marien Hospital, Stuttgart, Germany (by invitation). Discussion continued by: Charles J. Imperatori, Duncan Macpherson, Robert E. Buckley.

SECTION OF ORTHOPEDIC SURGERY—April 20

I. READING OF THE MINUTES.

II. PRESENTATION OF CASES—a. Some new apparatus in the treatment of fractures, George W. Hawley, Bridgeport (by invitation); b. A simple method for reduction of fracture dislocations of the vertebrae, especially those associated with spinal cord injuries, Byron Stookey; c. Cases demonstrating a new method of internal fixation in fractures of the neck of the femur using Kirschner wires, David Telson (by invitation).

III. PAPER OF THE EVENING—An analysis of end results in the treatment of central fractures of the neck of the femur and of the trochanteric region, J. S. Speed, Memphis (by invitation).

IV. General Discussion.

V. Executive Session—Nomination of Section officers and one member of Advisory Committee.

SECTION OF OBSTETRICS AND GYNECOLOGY—April 27

Program Arranged by the Obstetrical Staff of The Nursery and Child's Hospital.

(Meeting Postponed from April 24)

I. Reading of the Minutes.

II. Presentation of Cases—Rupture of a chocolate cyst with acute symptoms, Ogden F. Conkey (by invitation). Discussion: Howard C. Taylor, Jr.

III. Papers of the Evening—a. Placenta praevia—analysis of 146 cases, James P. Marr (by invitation). Discussion: Albert H. Aldridge. b. Pentobarbital analgesia—report of 200 cases, James P. Boylan (by invitation). Discussion: C. F. Jellinghaus, V. G. Damon (by invitation). c. Latzko-extra-peritoneal caesarean section—study of 79 cases, Henry T. Burns (by invitation). Discussion: Samuel J. Scadron.

IV. General Discussion.

V. Executive Session—Nomination of Section officers and one member of Advisory Committee.

AFFILIATED SOCIETIES

NEW YORK ROENTGEN SOCIETY IN AFFILIATION WITH THE NEW YORK ACADEMY OF MEDICINE

Monday Evening, April 16, at 8:00 o'clock

I. 8:00 to 8:30 p.m.—Demonstration and discussion of interesting cases.

II. 8:30 p.m.—Certain aspects of roentgenology of the spine from the orthopedic viewpoint, R. W. Lewis.

III. General Discussion—To be opened by Armitage Whitman (by invitation).

IV. Executive Session.

NEW YORK MEETING OF THE SOCIETY FOR EXPERIMENTAL BIOLOGY AND MEDICINE UNDER THE AUSPICES OF THE NEW YORK ACADEMY OF MEDICINE—April 18

I. Studies of incurable rickets. Respective role of the local factor and Vitamin D in healing, A. E. Sobel, A. Goldfarb, B. Kramer.

II. Experiments on Vitamin G concentration and possible supplementary relationships with Vitamin G deficient diet, J. W. Page, Jr. (Introduced by H. C. Sherman.)

III. Protection afforded by certain vegetable oils against nutritional encephalomalacia of chicks, A. M. Pappenheimer, M. Goettsch.

IV. Measurement of circulation time from antecubital veins to pulmonary capillaries, W. M. Hitzig. (Introduced by B. S. Oppenheimer.)

V. Pacinian corpuscles in the mesentery and their relation to the vascular system, G. D. Gammon, D. W. Bronk.

VI. Tuberculosis induced in the tadpole by feeding, J. F. Nonidez, M. C. Kahn.

VII. Globulin extract of immune adult serum in prophylaxis of measles, S. Karelitz. (Introduced by B. Schick.)

VIII. Prophylactic vaccination against intracranial complications following pneumococcus type III mastoiditis, G. Schwartzman, J. L. Goldman, C. Herschberger.

IX. New serum therapy for non-specific ulcerative colitis, G. Schwartzman, A. Winkelstein.

This was the annual meeting of the Society. Reports of tellers, secretary and treasurer were read.

RECENT ACCESSIONS TO THE LIBRARY

Abraham, J. J. Lettsom, his life, times, friends and descendants.
London, Heinemann, 1933, 498 p.

Association for research in nervous and mental disease. Localization of function in the cerebral cortex.
Balt., Williams, 1934, 667 p.

Atkinson, D. T. External diseases of the eye.
Phil., Lea, 1934, 704 p.

Beaumont, G. E. & Dodds, E. C. Recent advances in medicine. 7. ed.
London, Churchill, 1934, 485 p.

Best, H. Blindness and the blind in the United States.
N. Y., Macmillan, 1934, 714 p.

Brocq-Rousseu, D. & Roussel, G. Le sérum normal.
Paris, Masson, 1934, 363 p.

Byrne, J. G. Clinical studies on the physiology of the eye.
London, Lewis, 1934, 144 p.

Calmette, A.; Boquet, A. & Nègre, C. L. A. Manuel technique de microbiologie et sérologie. 3. éd.
Paris, Masson, 1933, 759 p.

Codman, E. A. The shoulder; rupture of the supraspinatus tendon and other lesions in or about the subacromial bursa.
Boston, [The Author?], 1934, 513 p.

Devine, H. Recent advances in psychiatry. 2. ed.
Phil., Blakiston, 1933, 364 p.

Dioscorides Anazarbeus, P. The Greek herbal of Dioscorides.
Oxford, Johnson, 1934, 701 p.

Feinberg, S. M. Allergy in general practice.
Phil., Lea, 1934, 339 p.

Fischer, G. Local anesthesia in dentistry. 4. ed.
London, Kimpton, 1934, 222 p.

Franklin, K. J. A short history of physiology.
London, Bale, 1933, 122 p.

Gadow, H. F. The evolution of the vertebral column.
Cambridge [Eng.], University Press, 1933, 355 p.

Gardner, A. D. Bacteriology, for medical students and practitioners.
London, Milford, 1933, 276 p.

Gask, G. E. & Ross, J. P. The surgery of the sympathetic nervous system.
Balt., Wood, 1934, 163 p.

Gastinel, P. & Pulvenis, R. La syphilis expérimentale.
Paris, Masson, 1934, 243 p.

Goodall, E. W. A short history of the epidemic infectious diseases.
London, Bale, 1934, 113 p.

Gutierrez, R. The clinical management of horseshoe kidney.
N. Y., Hoeber, 1934, 143 p.

Hanke, M. T. Diet and dental health.
Chic., Univ. of Chic. Press, [1933], 235 p.

Henning, N. Die Entzündung des Magens.
Leipzig, Barth, 1934, 235 p.

Howard, R. & Perry, A. C. The practice of surgery. 4. ed.
Balt., Wood, 1933, 1338 p.

Huddleson, I. F. Brucella infections in animals and man.
N. Y., Commonwealth Fund, 1934, 108 p.

Huxley, J. S. & De Beer, G. R. The elements of experimental embryology.
Cambridge [Eng.], University Press, 1934, 514 p.

Jungmichel, G. Alkoholbestimmung im Blut.
Berlin, Heymann, 1933, 124 p.

Key, J. A. & Conwell, H. E. The management of fractures, dislocations, and sprains.
St. Louis, Mosby, 1934, 1164 p.

Kovacs, R. Nature, M.D.
N. Y., Appleton-Century, 1934, 181 p.

Landsteiner, K. Die Spezifizität der serologischen Reaktionen.
Berlin, Springer, 1933, 123 p.

Leriche, R. & Stricker, P. L'artériectomie dans les artérites oblitérantes.
Paris, Masson, 1933, 194 p.

Lovejoy, E. P. Certain Samaritans. New ed.
N. Y., Macmillan, 1933, 344 p.

Mitchell, A. C. G. & Zemansky, M. W. Resonance radiation and excited atoms.
Cambridge [Eng.], University Press, 1934, 338 p.

Morse, W. R. Chinese medicine.
N. Y., Hoeber, 1934, 185 p.

Muir, R. Text-book of pathology. 3. ed.
Balt., Wood, 1933, 957 p.

National organization for public health nursing. Committee on field studies and administrative practice. Survey of public health nursing; administration and practice.
N. Y., Commonwealth Fund, 1934, 262 p.

Newsholme, (Sir) A. & Kingsbury, J. A. Red medicine; socialized health in Soviet Russia.
Garden City, Doubleday, 1933, 324 p.

Nicolaysen, J. Kirurgien i Norge i det 19de århundre.
Oslo, Centraltrykkeriet, 1933, 127 p.

Nissen, N. I. Studies on alimentary lipaemia in man.
Copenhagen, Levin, 1933, 176 p.

Obermeyer, H. Stop that smoke.
N. Y., Harper, 1933, 289 p.

Oldham, F. Thomas Young, F.R.S., philosopher and physician.
London, Arnold, 1933, 159 p.

Pachon, V. & Fabre, R. Clinical investigation of cardiovascular function.
London, Paul, 1934, 252 p.

Pal, J. Die Tonuskrankheiten des Herzens und der Gefässe.
Wien, Springer, 1934, 228 p.

Park, W. H. & Williams, A. W. Pathogenic microörganisms. 10. ed.
Phil., Lea, [1933], 867 p.

Pattee, A. F. Practical dietetics. 19. ed.
Mt. Vernon, Pattee, 1933, 881 p.

Payr, E. Gelenksteifen und Gelenkplastik.
Berlin, Springer, 1934, pt. 1.

Pearl, R. Constitution and health.
London, Paul, 1933, 97 p.

Philips' (N. V.) gloeilampenfabrieken, Eindhoven. X-ray research and development. A selection of publications of the Philips x-ray research laboratory.
London, Hanbury, [1934?], 204 p.

Renshaw, S.; Miller, V. L. & Marquis, (Mrs.) D. (Postle). Children's sleep.
N. Y., Macmillan, 1933, 242 p.

Seaver, G. Edward Wilson of the Antarctic.
London, Murray, [1934], 301 p.

Seldin, H. M. Practical anesthesia for dental and oral surgery.
Phil., Lea, 1934, 525 p.

Stinchfield, S. M. Speech disorders.
London, Paul, 1933, 341 p.

Textbook (A) of the practice of medicine. Edited by F. W. Price. 4. ed.
London, Milford, 1933, 1995 p.

Thomson, J. The clinical study and treatment of sick children. 5. ed.
Edinburgh, Oliver, 1933, 1075 p.

Traité élémentaire d'exploration clinique médicale (technique et séméiologie). Publié sous la direction de E. Sergent.
Paris, Masson, 1934, 1176 p.

de Vries, W. M. Atlas of selected cases of pathological anatomy.
Amsterdam, de Bussy, 1933, 73 p.

Wakeley, C. P. G. & Hunter, J. B. Rose and Carless' manual of surgery. American (14.) ed.
Balt., Wood, 1933, 1408 p.

Walker, K. M. The enlarged prostate and prostatic obstruction. 2. ed.
London, Milford, 1933, 223 p.

Watson, F. The life of Sir Robert Jones.
London, Hodder, 1934, 327 p.

Wollaston, A. F. R. Letters and diaries.
Cambridge [Eng.], University Press, 1933, 261 p.

AMENDMENT TO BY-LAWS PASSED AT A STATED MEETING OF THE ACADEMY HELD MARCH 1, 1934

ARTICLE X, SECTION 7

as prepared by the counsel of the Academy

and presented by the Trustees.

SECTION 7. *Executive Committee.* The Board of Trustees by resolution passed by a majority of the whole Board, may designate two or more of their number to constitute an Executive Committee to serve during the pleasure of the Board. During the interval between the meetings of the Board of Trustees the Executive Committee shall possess and may exercise all of the powers of the Board of Trustees conferred by these by-laws or otherwise, except as limited from time to time by resolution of the Board of Trustees, including power to authorize the seal of the Corporation to be affixed to all papers which may require it. The Committee shall adopt its own rules of procedure, and shall meet when and where and according to the notice provided by such rules. It shall keep a record of all its proceedings and report the same to the Board of Trustees.

Vacancies in the Executive Committee shall be filled by the Board of Trustees, but during the temporary absence or inability to act of a member of the Executive Committee, the remaining members may appoint a member of the Board of Trustees to act in his place. The members of the Committee shall elect one of their number as Chairman, and may elect another member as Vice-Chairman. The Secretary or any other official of the Corporation shall perform the duties of Secretary to the Committee at its request. A majority of the Committee shall constitute a quorum.

FELLOW AND MEMBERS AND ASSOCIATE ELECTED MARCH 1, 1934

Fellow:

Birt Lee Browning.....Grand Ave., Balaville, N. Y.

Members:

Ruth Morris Bakwin.....132 East 71 Street
Sandor Lorand.....115 East 86 Street
Frances Emily Shields.....5 East 57 Street
Russell C. Kimball.....52 Remsen St., Brooklyn
Willis Sackett Knighton.....40 East 61 Street
George Eaton Daniels.....454 Riverside Drive
Lester Reginald Tuchman.....101 West 58 Street
Bertram David Lewin.....25 Fifth Avenue

Associate:

Robert Keith Cannan, M.Sc.....477 First Avenue

FELLOWS AND MEMBERS ELECTED

APRIL 5, 1934

Fellows:

Jacob E. Holzman.....1075 Park Avenue
Otho C. Hudson.....Hempstead, L. I.

Members:

John L. Rice.....Department of Health
Louis Wender.....Hastings-on-Hudson, N. Y.
Olin Everett Farley.....140 East 54 Street
Phil Hawkins Neal.....136 East 65 Street
Joseph Benjamin Stenbuck.....1165 Park Avenue
Seymour H. Silvers.....2 East 54 Street
Peter G. Denker.....139 East 66 Street
Virgil G. Damon.....1088 Park Avenue
Tibor de Cholnoky.....35 East 84 Street
John Corran McCauley, Jr.....116 East 63 Street
Gustave Aufricht.....103 East 86 Street

DEATHS OF FELLOWS OF THE ACADEMY

Cleveland, Clement, M.D., 11 West 11 Street, New York City; graduated in arts from Harvard University in 1867 and in medicine from the College of Physicians and Surgeons, New York City, in 1871; elected a Fellow of the Academy May 1, 1879; died, April 16, 1934. At the time of his death he was the oldest living Fellow of the Academy. He was a Trustee of the Academy from 1897 to 1900. Dr. Cleveland was a Fellow of the American College of Surgeons. He was formerly President of the American Gynecological Society and of the New York Obstetrical Society. At various times he was connected with Woman's Hospital and Memorial Hospital and from 1882 to 1915 he was Attending Surgeon and Surgical Director of City Hospital.

Ely, Albert Heman, M.D., Cold Spring Harbor, Long Island, New York; graduated in medicine from the College of Physicians and Surgeons in 1888; elected a Fellow of the Academy March 1, 1894; died April 26, 1934. Dr. Ely was a Fellow of the American Medical Association and a member of the County and State Medical Societies, the New York Obstetrical Society and the Alumni Association of St. Luke's Hospital. He was at one time associated with Roosevelt and City hospitals. He was one of the founders of Southampton Hospital where he was consulting surgeon at the time of his death.

PACKARD, MAURICE, Ph.B., M.D., 17 West 70 Street, New York City; graduated in medicine from the College of Physicians and Surgeons, New York City, in 1900; elected a Fellow of the Academy February 4, 1909; died, March 14, 1934. Dr. Packard was a Fellow of the American Medical Association, a member of the County and State Medical Societies, the New York Pathological Society and the Brooklyn Hospital Alumni Association. He was Consulting Physician to Joint Diseases, Broad Street and Jewish Maternity hospitals and Physician to Gouverneur Hospital.

PILGRIM, CHARLES WINFIELD, M.D., Central Valley, New York; graduated in medicine from Bellevue Hospital Medical College in 1881; elected a Fellow of the Academy October 6, 1898; died May 3, 1934. Dr. Pilgrim was a member of the County and State Medical Societies, the American Psychiatric Association and the Psychiatric Society of New York. Dr. Pilgrim was a pioneer in the development of the out-patient department in connection with the State hospitals and was one of he earliest advocates of mental clinics and social service work among the insane. He also urged extension of the parole system among the insane. In recognition of the outstanding service performed by Dr. Pilgrim in the State hospitals and among the insane of New York State, the New York State Legislature in 1929 authorized construction of the Charles W. Pilgrim State Hospital at Brentwood, New York, which will be the largest asylum in the world when it is completed.